Schizophrenia Research 152 (2014) 255–260

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Olanzapine and clozapine differently affect sleep in patients with schizophrenia: Results from a double-blind, polysomnographic study and review of the literature

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ARTICLE INFO

Article history:
Received 29 July 2013
Received in revised form 4 November 2013
Accepted 11 November 2013
Available online 5 December 2013

Keywords:
Sleep
REM
Slow-wave-sleep
Olanzapine
Clozapine
Restless legs syndrome
RLS

ABSTRACT

Schizophrenia is associated with impaired sleep continuity. The second generation antipsychotics clozapine and olanzapine have been reported to improve sleep continuity but also to rarely induce restless legs syndrome (RLS). The aims of this randomized double-blind study were to compare the effects of clozapine and olanzapine on sleep and the occurrence of RLS. Therefore, polysomnographies were recorded and RLS symptoms were assessed in 30 patients with schizophrenia before and after 2, 4 and 6 weeks of treatment with either clozapine or olanzapine. Treatment with both antipsychotics increased total sleep time, sleep period time and sleep efficiency and decreased sleep onset latency. These changes were similar in both groups, occurred during the first 2 treatment weeks and were sustained. For example, sleep efficiency increased from 83% (olanzapine) and 82% (clozapine) at baseline to 95% at week 2 and 97% at week 6 in both treatment groups. Sleep architecture was differently affected: clozapine caused a significantly stronger increase of stage 2 sleep (44%) than olanzapine (11%) but olanzapine a significantly stronger increase of REM-sleep. Olanzapine caused an 80% increase of slow wave sleep whereas clozapine caused a 6% decrease. No patient reported any of 4 RLS defining symptoms at baseline. During treatment, 1 patient of each group reported at one visit all 4 symptoms, i.e. met the diagnosis of an RLS. In conclusion, sleep continuity similarly improved and sleep architecture changed more physiologically with olanzapine. Neither of the antipsychotics induced RLS symptoms that were clinically relevant.

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1. Introduction

Sleep in patients with schizophrenia is impaired comparing to healthy subjects. Delayed sleep onset, decreased total sleep time and reduced sleep efficiency are the most consistent findings from studies in drug naïve patients. In addition, several studies demonstrated a shorter REM latency and less slow wave or non-REM stage 4 sleep in drug naïve patients than healthy controls (Cohrs, 2008; Monti et al., 2013). Sleep disturbances affect up to 80% of patients with schizophrenia (Cohrs, 2008) and are associated with impaired cognitive functioning (Bromundt et al., 2011), decreased quality of life (Hofstetter et al., 2005) and severity of illness (Sarkar et al., 2010). Therefore, improvement of sleep disturbance is an important goal in the treatment of patients with schizophrenia.

The second generation antipsychotics (SGAs) clozapine and olanzapine share similar receptor binding patterns (Bymaster et al., 1996), good efficacy (Leucht et al., 2013), unfavourable metabolic side effects (Rummel-Kluge et al., 2010) but a favourable extrapyramidal side effect profile (Rummel-Kluge et al., 2012). In addition, several sleep-EEG studies, mostly open, suggested a sleep-improving effect of olanzapine and clozapine (Rüther et al., 1976; Touyz et al., 1977, 1978; Wetter et al., 1996; Hinze-Selch et al., 1997; Salin-Pascual et al., 1999; Sharpley et al., 2000; Lee et al., 2001; Lindberg et al., 2002; Armitage et al., 2004; Müller et al., 2004; Salin-Pascual et al., 2004; Sharpley et al., 2005; Gimenez et al., 2007; Moreno et al., 2007; Göder

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http://dx.doi.org/10.1016/j.schres.2013.11.009

et al., 2008). However, there are no double-blind studies in patients with schizophrenia investigating sleep effects of these related antipsychotics (Table 1).

Falling asleep can be disturbed by a restless legs syndrome (RLS), defined by four essential criteria: an urge to move the legs, usually accompanied by unpleasant sensations; worsening during periods of rest or inactivity; a partial or total relief by movement, and worsening in the evening or during the night (Allen et al., 2003; Leschziner and Gringras, 2012). While some case reports suggest that clozapine (Duggal and Mendhekar, 2007; Chathanchirayil, 2011) or olanzapine (Kraus et al., 1999; Kang et al., 2009; Khalid et al., 2009; Aggarwal et al., 2010) may be associated with RLS, corresponding prospective studies are lacking.

Therefore, the aims of this randomized double-blind study were to determine sleep parameters and occurrence of RLS before and after 2, 4 and 6 weeks of treatment with either clozapine or olanzapine. In addition, we carried out a review of the literature on sleep-EEG studies investigating these drugs.

2. Materials and methods

2.1. Patients

Male or female inpatients, 18 to 65 years old, meeting DSM-IV diagnostic criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder were included. Furthermore, inclusion criteria comprised a Brief Psychiatric Rating Scale (BPRS) $_{0-6}$ score of ≥ 24. Patients with clinical signs of sleep apnea such as excessive daytime sleepiness or pauses in breathing were not considered for this study. Exclusion criteria comprised any serious, unstable physical illness, uncorrected hypothyroidism, narrow-angle glaucoma, leukopenia, history of one or more seizures, current jaundice, or any concomitant medication with primary activity on the central nervous system (CNS). All patients signed written informed consent. Ethical review board approval was obtained.

2.2. Study design

This was a randomized, double-blind single-center study. Patients underwent a 2–9 day screening and wash-out period, followed by a six-week double-blind treatment period. At visit 1, the patients' medical and psychiatric history was taken, and physical examination and screening tests were performed. At visit 2 (baseline), patients were randomly assigned to a double-blind treatment with either olanzapine 5–25 mg or clozapine 100–400 mg daily. During the first two weeks of treatment, the dose range was restricted (olanzapine 10–15 mg, clozapine 25–200 mg daily). Both treatment groups received capsules in the morning and evening. However, the complete verum dose of olanzapine and the main verum dose of clozapine respectively were administered in the evening. Patients treated with clozapine received a maximum of 50 mg/day in the morning. Concomitant psychotropic medication was not permitted except for benzodiazepines during the first 2 treatment weeks (maximum: 40 mg diazepam equivalents/day). Coffee was restricted to one cup per day on the days when polysomnographies were performed. Daytime sleep was not allowed. In order to ensure this, patients were observed during the day.

Efficacy and tolerability ratings (e.g. Brief Psychiatric Rating Scale [BPRS]; Simpson–Angus Scale [SAS]), adverse events, routine laboratory parameters, and cytokine plasma levels were assessed weekly, whilst sleep propensity at daytime using multiple sleep latency tests (MSLT) was assessed every other week. The results of these assessments are described elsewhere. Both antipsychotics were shown to be equally efficacious (Kluge et al., 2007a, 2009, 2012).

2.3. Sleep recordings

Polysomnography comprised EEG, vertical and horizontal electrooculograms, an electromyogram (anterior tibialis muscles) and ECG (Comlab 32 Digital Sleep Lab, Schwarzer GmbH, Munich, Germany). Polysomnographic recordings were conducted according to standard procedures at baseline and after 2, 4 and 6 weeks of treatment, each following an adaptation night in the sleep laboratory. Polysomnography started at 2300 h when lights were switched off and stopped 8 h later, when subjects were awakened. Sleep recordings were scored visually in 30 s epochs according to Rechtschaffen and Kales by experienced raters blind to condition (Rechtschaffen and Kales, 1968). The raters took care to consider that both olanzapine and clozapine may cause signs of EEG slowing while still awake (Schuld et al., 2000; Wichniak et al., 2006). The following sleep variables were calculated: sleep period time (SPT, time from first epoch containing stage 2 sleep until final awakening), total sleep time, sleep onset latency (time between lights off and first occurrence of stage 2 sleep), REM latency (interval between sleep onset and first epoch containing REM sleep), slow wave sleep (SWS) latency (interval between sleep onset and first epoch containing stage 3 sleep), sleep efficiency (TST/SPT × 100), REM density (mean number of 3-s mini-epochs containing rapid eye movements/30 s

Table 1
Sleep-EEG studies in subjects treated with olanzapine or clozapine.

Olanzapine	Diagnosis	N	Study design	Main Results
Kluge, this study	schizophrenia	15	random., db, parallel; BL, Wk 2, Wk 4, Wk 6	TST↑, SE↑, SOL↓, REML(↓), S1=, S2↑, SWS↑↑, REM↑
Göder et al., 2008	schizophrenia	13	random., sb, BL, Night 1; add-on to amisulpride	TST=, SE=, SOL↓, REML?, S1?, S2↑, SWS↑↑, REM↓
Moreno et al., 2007	mania	7	random., db, parallel; BL; ~ Wk 6	TST=, SE=, SOL=, REML=, S1=, S2=, SWS=, REM=
Gimenez et al., 2007	healthy subjects	17	random., db, cross-over: pl., 5 mg	TST↑, SE↑, SOL=, REML=, S1↓, S2=, SWS↑↑, REM↑
Sharpley et al., 2005	depression	12	open; BL, Night 1, Wk 3; add-on to SSRI	TST↑, SE↑, SOL↓, REML↑/=, S1=, S2=, SWS↑, REM=
Salin-Pascual et al., 2004	schizophrenia	18	open, BL, Night 1, Night 2	TST↑, SE?, SOL↓, REML?, S1↓, S2=, SWS↑, REM↓/=
Müller et al., 2004	schizophrenia	10	open, BL, Wk 4	TST↑, SE↑, SOL↓, REML=, S1=, S2=, SWS↑↑, REM↑
Lindberg et al., 2002	healthy subjects	13	open, single dose; BL, Night 1	TST↑, SE=, SOL↓, REML=, S1=, S2=, SWS↑↑, REM↑
Sharpley et al., 2000	healthy males	9	random., db, cross-over: pl., 5 mg, 10 mg	TST↑, SE↑, SOL↓, REML↑, S1↓, S2=, SWS↑↑, REM↓
Salin-Pascual et al., 1999	schizophrenia	20	open, BL, Night 1, Night 2	TST↑, SE↑, SOL↓, REML=, S1↓, S2↑, SWS↑↑, REM=
Clozapine				
Kluge, this study	schizophrenia	14	random., db, parallel; BL, Wk 2, Wk 4, Wk 6	TST↑, SE↑, SOL↓, REML=, S1=, S2↑↑, SWS↓/=, REM↑
Armitage et al., 2004	bipolar disorder	14	open, BL, Month 6; add-on to mood stabilizers	TST↑, SE=, SOL↑, REML=, S1=, S2=, SWS=, REM=
Lee et al., 2001	schizophrenia	5	open, BL, Day 4; Wk 6 to 8	TST↑, SE↑, SOL=, REML=, S1=, S2↑, SWS=, REM=
Hinze-Selch et al., 1997	schizophrenia	10	open; BL, Wk 1, Wk 2	TST↑, SE↑/=, SOL=, REML=, S1=, S2↑↑, SWS↓, REM=
Wetter et al., 1996	schizophrenia	12	open; no BL, Wk 2 comparison with sleep in drug-naive patients	TST↑, SE↑, SOL↓, REML=, S1=, S2↑↑, SWS=, REM=
Touyz et al., 1978	healthy males	6	sb, cross-over, 12.5 mg clozapine	TST=, SE = SOL=, REML=, S1↓, S2=, SWS=, REM↓
Touyz et al., 1977	healthy males	7	db, parallel, pl., 25 mg clozapine	TST↑, SE = SOL=, REML=, S1=, S2=, SWS=, REM=
Rüther et al., 1976	schizophrenia	6 (2)	open, BL; Night 7, Night 14	TST?, SE?, SOL?, REML?, S1?, S2?, SWS↓, REM↑

db: double-blind; sb: single-blind, BL: baseline; pl.: placebo; ↑: significant increase; ↓: significant decrease; =: no significant difference; ?: not reported;
TST: total sleep time; SE: sleep efficiency; SOL: sleep onset latency; REML: REM latency; SWS: slow wave sleep; S1: stage 1 sleep; S2: stage 2 sleep.

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