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Sleep architecture in insomniacs with severe benzodiazepine abuse

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HIGHLIGHTS

- Long term abuse of benzodiazepines induced only mild alterations of sleep architecture.
- A depression of slow wave power activity during NREM sleep occurred in benzodiazepine abusers.
- A suppression of the cyclic alternating pattern rate was the main finding in benzodiazepine abusers.

ABSTRACT

Objective: Benzodiazepines (BZDs) are the most commonly prescribed compounds in insomnia. A long-term of BZDs use may cause dependence and abuse. The aim of this study was to evaluate sleep architecture and microstructure (in terms of cyclic alternating pattern – CAP – analysis and of sleep EEG power spectral analysis) in a group of long-term users of high doses of BZDs for their primary chronic insomnia.
Methods: Twenty patients consecutively admitted at the Sleep Centre for drug discontinuation and 13 matched healthy controls underwent a full nocturnal video-polysomnographic recording, after one adaptation night.
Results: Significant differences were found in time in bed, REM sleep latency and sleep stage 1% which were increased in patients compared to controls, while CAP rate was dramatically decreased. During NREM sleep, patients showed a clear decrease in the relative power of delta band.
Conclusions: Our data demonstrate that in adults with chronic insomnia, long-term use of high doses of BZDs induces a severe disruption of sleep microstructure, while sleep architecture seems to be much less affected.
Significance: The long term use of high doses of BZDs for chronic insomnia induces a marked depression of slow wave activity and of its physiological instability.

1. Introduction

Benzodiazepines (BZDs), and non-BDZ $GABA_A$ receptor agonists are among the most commonly prescribed treatment for insomnia disorder. In general, BZDs are safe and effective as a short term treatment of insomnia, but their long-term use may cause abuse and its complications such as addiction, intoxication and abstinence (Woods et al., 1992). If dependence can be diagnosed in most patients undergoing long therapeutic BDZs treatment, the switch to an addicted state only occurs in less than 10% of users (Woods et al., 1992). Addiction is defined by the World Health Organisation as a compulsive substance intake despite negative consequences, characterised by relapse after a prolonged period of abstinence (Lalive et al., 2011). Few studies have been published reporting a cognitive impairment related to the long term intake of BZDs, such as impairment of visuospatial ability, speed of processing, and verbal learning (Barker et al., 2004).

Sleep architecture and sleep microstructure of drug-free insomnia suffers, and the positive effects of a short term treatment with hypnotic compounds have been extensively studied. Several studies examined the sleep EEG power spectra in drug-free insomnia patients and have demonstrated an overall increase of fast activities (for details see the review by Bastien, 2011), a reduction of wake

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time after sleep onset, an increase of sleep efficiency and of total sleep time, after short term treatment with BZDs (Morin et al., 1999). However, more than the macrostructure of sleep, it is the microstructure to be mainly affected in primary chronic insomnia. In particular, in the last two decades, polysomnographic studies on insomnia have been focused on the analysis of the so-called cyclic alternating pattern (CAP), that is considered a solid marker of NREM sleep instability (Parrino et al., 2008). CAP is an endogenous infra-slow rhythm occurring during NREM sleep, consisting of oscillating transient activating complexes (phase A) that periodically interrupt the tonic theta/delta activities of NREM sleep (phase B). More specifically, the percentage of NREM sleep occupied by this oscillating CAP process (CAP rate) is considered the physiologic marker of NREM sleep instability, ranging between 30 and 38% in normal adults and going up in insomniacs. CAP A phases have been subdivided into different subtypes: A1, A2 and A3, based on their frequency content (Terzano et al., 2001). Subtype A1 is composed predominantly by slow waves (EEG synchrony), subtype A3 shows a prevalence of fast EEG activities (EEG desynchrony), and subtype A2 presents a combination of the other two subtypes. A1 subtypes are involved in the build-up and maintenance of slow-wave NREM sleep and have a protective role for sleep continuity, as a sort of "antiarousals" (Hirshkowitz, 2002), on the other hand, A2 and A3 herald REM sleep and have the function of maintaining the subject arousability (Terzano et al., 2001). Exogenous or endogenous disturbing factors of different nature exert a common destabilizing action on sleep, consisting in an increase of CAP rate (especially subtype A2 and A3), which correlates with the subjective sleep complains (Terzano et al., 2003a). Effective hypnotic treatment restores a physiological amount of CAP rate, with specific differences between the administered drugs (Terzano et al., 2003b), and after an acute administration (Parrino et al., 1997) or after a short term treatment (Parrino et al., 2008). Despite the clinical evidence of tolerance, definable as an adaptation to a substance so that increasingly larger doses are required to produce the same effect, the impact of the long term use of BZDs for the treatment of insomnia have been poorly investigated. One study examined power spectral analysis of sleep EEG, in older adults with insomnia disorder and chronic use of BZDs, compared to good-sleepers and to drug-free insomniacs (Bastien et al., 2003). The authors found that BZDs users exhibited significant sleep microstructure alterations compared to both controls and drug-free insomnia sufferers, consisting of a reduction in delta and theta activity and an increase in beta activity during sleep (Bastien et al., 2003). In a small group of 6 insomniac patients with BZD abuse significant alterations of sleep microstructure with a reduction of CAP rate have been highlighted (Mazza et al., 2014).

These results raise important questions about the effects and indications of the prolonged use of this type of medications in insomnia, suggesting that a long term intake of BZDs have negative effect on sleep. Literature on sleep changes in insomniacs with chronic abuse with high doses of BZDs is substantially inexistent.

The aim of our study was to evaluate sleep architecture and sleep microstructure (CAP analysis and power spectral analysis of sleep) in a group of adults with chronic insomnia disorder and under a long term abuse of high doses of BZDs, consecutively admitted to Sleep Disorders Center of Vita-Salute San Raffaele University, Milan, for drug wash-out.

2. Subjects and methods

2.1. Subjects

Adults with a diagnosis of chronic primary insomnia according to the International classification of sleep disorders, revised (ICSD, 2014), and further diagnosis of abuse of BZDs, both of them ascertained by using the DSM-V criteria (2013), were included in the study. Additional inclusion criteria were a daily intake of BZDs at least 2-fold higher than the maximum recommended dosage, for at least 3 months before the time of enrolment. Patients were prospectively and consecutively selected among those admitted to the Sleep Disorders Center, Ospedale San Raffaele, Milan, for discontinuation of therapy. Considering that some patients may use more than one type of BZD, an equivalent dose of diazepam was determined for each patient, according to the Bazire conversion scale (1994).

All patients underwent a full psychiatric, neurological and medical evaluation, and were excluded if they had other known sleep disorders, a Mini-Mental State Evaluation score <24 (Folstein et al., 1983) a diagnosis of an active psychiatric disorder other than abuse/dependence or of any other medical conditions that would affect sleep.

All patients underwent a nocturnal polysomnographic recording, after one adaptation night, at the beginning of their hospitalization, while they were still taking high doses of BZDs.

Subjective sleep quality and sleep disturbances were defined by the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), while the dependence from drugs was established with the Severity Dependence Scale (SDS), with a cut off score above 6 (Gossop et al., 1995).

Patient sleep parameters were compared to those of a control group of healthy untreated volunteers, matched for age and sex, who underwent a full medical, psychiatric and neurological evaluation and a polysomnographic recording after one adaptation night.

All participants gave their written consent for these procedures. The local ethical committee approved the study.

2.2. Nocturnal polysomnography

"Nocturnal polysomnography was carried out in a standard sound-attenuated (noise level to a maximum of 30 dB normal hearing level, nHL) sleep laboratory room. Subjects were not allowed caffeinated beverages the afternoon preceding the recordings and were allowed to sleep in until their spontaneous awakening in the morning. Light-out time was based on individual habitual bedtime and ranged between 10.30 and 11.30 p.m. The following signals were recorded: EEG (at least 6 channels, including C3 and C4, referred to the contralateral mastoid); electrooculogram (electrodes placed 1 cm above the right outer cantus and 1 cm below the left outer cantus and referred to the left mastoid), electromyogram (EMG) of the submentalis muscle, EMG of the right and left tibialis anterior muscles (bipolar derivations with two electrodes placed 3 cm apart on the belly of the tibialis anterior muscle of each leg, impedance was kept less than 10 KΩ, and ECG (CM4 derivation: anode in position V4 and cathode attached to the manubrium of the sternum). Sleep signals were sampled at 200 Hz and stored on hard disk in European data format for further analysis" (Plazzi et al., 2014).

2.3. Sleep scoring and CAP analysis

Sleep stages and periodic leg movements were scored following standard criteria and the periodic leg movements index was quantified as their number per hour of sleep (Rechtschaffen and Kales, 1968; Zucconi et al., 2006).

"Each CAP A phase was detected on the C3/A2 or C4/A1 derivation; the side of this EEG channel should not influence the detection of CAP because CAP components have been shown to map symmetrically over the scalp" (Ferri et al., 2005a). "All CAP phases during NREM sleep were detected and classified into three subtypes (A1, A2, and A3). CAP is a periodic EEG activity in NREM sleep