Sleep disorders with antipsychotic drugs: based on one case with clozapine

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Alteraciones del sueño con los antipsicóticos: a propósito de un caso con clozapina

Summary

Clozapine is a widely used atypical neuroleptic in the treatment of schizophrenia; its effects on sleep have been poorly studied, sedation being one of its side effects.

We present the case of hypersomnia and marked reduction of REM sleep secondary to treatment with clozapine and review existing scientific literature on the action of neuroleptics on sleep.

Key words: *Clozapine. REM sleep. Hypersomnia.*

Resumen

La clozapina es un neuroléptico atípico ampliamente utilizado en el tratamiento de la esquizofrenia, cuyos efectos sobre el sueño han sido escasamente estudiados, siendo la sedación uno de sus efectos secundarios.

Presentamos el caso de una hipersomnia y reducción marcada de la fase REM del sueño secundarias al tratamiento con clozapina y revisamos la literatura existente sobre la acción de los neurolépticos sobre el sueño.

Palabras clave: *Clozapina. Sueño REM. Hipersomnia.*

INTRODUCTION

Since Aserinsky and Kleitman[1] first described REM sleep in 1953 in children, sleep has become considered an active and complex phenomenon that merits increasing attention from neurophysiologists and clinicians. In spite of recent investigations, it is still not known what brain areas initiate and end sleep, although the areas and neurotransmitters involved in its physiology are known generically.

Thus we know that the cholinergic system participates in the regulation of wakefulness, but also in the control of NREM sleep onset, and noradrenaline facilitates the onset of REM sleep. Both the noradrenergic neurons of the locus coeruleus as well as the serotoninergic ones of the raphe decrease their activity during NREM sleep and become silent in the REM phase. Serotoninergic neurons have a complex role in the physiology of sleep, since they remain active in wakefulness, but their inactivation paradoxically implies insomnia. The histaminergic system participates in the control of wakefulness from its neurons located in the ventrolateral posterior hypothalamus and the GABAergic system (Meynert nucleus) also plays an essential role in the regulation of slow wave sleep.

There are also other neuro-hormonal substances responsible for sleep regulation whose functions have not been sufficiently established, such as prostaglandin D2, vasoactive intestinal peptide (VIP), growth hormone (GH), growth hormone-releasing factor (GRF), somatostatin, vasotocin, etc.

SLEEP IN SCHIZOPHRENIA

Sleep disorders in patients with schizophrenia are well known by the clinicians, but have received little attention in the scientific literature. Haffmans et al.[2] report complaints of sleep problems in 37.6 % of the patients studied by them: 26 % complained of having trouble falling asleep, 23 % of middle insomnia and 16 % of early waking. A total of 35.5 % of the patients received treatment with hypnotics and 23 % did not receive any treatment for sleep disorders.

The starting point of the studies on the sleep disorders in schizophrenia was based on the hypothesis that stated that it could be an intrusion of sleep in wakefulness similar to the halluninatory phenomena that occur in narcolepsy due to the similarities existing between dreaming and psychosis (in dreams, hallucinations, perceptual distortions, rare thinking and temporary delusions are mixed with normal perceptual processes and thoughts).

The first polygraphic sleep studies in schizophrenia did not find any evidence of important disorders in REM

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sleep or of the intrustion of phenomena of the REM phase in wakefulness in these patients (Dement[3], 1955). Koresko et al.[4] found few differences between REM sleep of patients with and without hallucinations, while Jus et al.[5] found shorter REM periods, more frequently interrupted by waking up in untreated schizophrenic subjects and paired by age groups compared to controls, although the total time of the REM sleep in schizophrenics and controls did not differ significantly.

Another variable of REM sleep studied in schizophrenia was REM latency. The data are contradictory, some studies mentioning a shortened REM latency while others that used strict criteria of schizophrenia and strict definitions of latency did not find any differences with control subjects, and this subject is not yet solved.

All of that presented above makes it possible to conclude that a single or specific alteration of the REM phase does not seem to exist in schizophrenics.

It is also postulated that REM sleep rebound in schizophrenia after sleep deprivation is abnormal (absent or reduced). Zarcone et al.[6] supported these results in his investigations with acute and chronic patients. The studies (two) that do not find REM sleep rebound disorders after sleep deprivation have important methodological problems. We stress that in the study of sleep, the variations that influence the data analysis, such as the phase of the disease (acute or chronic phase), if the patients receive drug treatment or not, as well as the heterogeneity itself of schizophrenia, must be kept in mind.

Another piece of data mentioned in many studies is the reduction of slow wave sleep, especially in the first half of the cycle, data that could be retorted in other studies. It has also been seen that sleep stage 4 amplitude was much less in schizophrenics than in controls and the elderly, presenting higher NREM sleep frequencies than in the controls and elderly in the analysis of frequencies in the first half of the night. On the contrary to the controls, schizophrenics with less stage 4 sleep do not show stage 4 sleep rebound after total sleep deprivation[7,8]. All this indicates a deficit in stage 4 sleep in patients with schizophrenia whose clinical significance is unknown. Some authors indicate that stage 4 correlates with REM phase latency in both schizophrenia as well as in schizoaffective disorders and depression. This could mean that REM latency is shortened due to a problem in the first NREM period[9-14].

There are also data that come from treatment with neuroleptics, since these increase slow wave sleep. In regards to the latter, we should remember that:

- — Neuroleptics increase slow wave sleep through their weak effect on temperature regulation.
- — Slow wave sleep is important in the regulation of temperature.
- — Compared with normal persons, schizophrenics may have a disorder in circadian regulation of temperature manifested by a high temperature peak in the morning and a decrease below the minimum at night[15].

Thus, the abnormality observed in the slow wave sleep of these patients may be related with a parallel disorder in temperature regulation.

It has also been suggested that delta sleep disorders are associated with negative symptoms, premorbid deterioration, increase of ventricles and attention deterioration, these being symptoms that are related with a poor prognosis in schizophrenia. Keshavan et al.[16] found a positive and significant correlation between these disorders, a poor prognosis, poor electrodermal response and poor response to neuroleptics. This author[17] states that there is a reduction in delta sleep in first episode schizophrenic patients not taking medication, which suggests that this abnormality is a primary phenomenon and not a simple epiphenomenon.

Delta sleep disorders have been related with negative symptoms and frontal deterioration of the cerebral metabolism, and have been related with the theory of the development of schizophrenia.

In addition, it has been observed that patients with an early onset of schizophrenia have less sleep alteration[18].

Keshavan et al.[19] conclude that the most frequent sleep abnormalities of the schizophrenics are:

- — A reduction in total sleep time.
- — A reduction in delta sleep percentage.
- — A reduction in REM sleep latency in some patients.
- — A reduction in the compensation phenomena that follow sleep deprivation.
- — A reduction in sleep efficiency and maintenance.
- — An increase in REM sleep in some patients.

A sleep regulation deficit of schizophrenics has also been mentioned[20].

NEUROLEPTICS AND SLEEP

Neuroleptics have no characteristic effects on sleep at therapeutic doses, although they tend to reduce wakenings and increase slow wave sleep through their weak effect on temperature regulation.

Their effect on REM sleep is more complex: thus low doses of chlorpromazine increase REM, possibly by alpha 2 antagonism, while REM sleep is reduced at higher doses in which the action on the alpha 1 post-synaptic receptors predominates.

Suppression of the REM sleep phase by some neuroleptics is due to their anticholinergic action, since they reduce REM sleep as antagonists of the muscarinic receptors.

It has also been observed that when neuroleptics are discontinued, there is deterioration of REM and NREM sleep and reduction of REM latency, of sleep efficiency, of total sleep and of stage 2 sleep.

Within the atypical neuroleptics, it has been observed that olanzapine reduces wakefulness, does not alter structure and continuity of sleep, increases slow wave sleep perhaps by acting on the 5-HT(2C) receptors[21,22], reduces stage 1 and increases stage 2 and REM density[23].

Studies with risperidone point out that this reduces the wakefulness level and significantly reduces the sleep REM phase[24] and acts on slow wave sleep, reducing it less than haloperidol[25] in humans. In rats, it increases deep sleep, and decreases mild slow wave sleep, while it produces opposite effects at high doses.[26]

We have not found specific studies on sleep with the most recent antipsychotics.

CLOZAPINE AND SLEEP

Clozapine was approved for use in psychiatry by the Food and Drug Administration in 1989 and has been widely used since then all over the world. However, there are few and not very clarifying studies on its side effects on sleep, neurotransmitters and endocrine parameters.

Clozapine, neurotransmitters and hormones

Clozapine, described as an atypical antipsychotic, is a dibenzodiazepine, that has relatively limited potency as type D2 dopaminergic receptor antagonists, mean potency on muscarinic and histaminergic (H1) receptors and greater potency on the D1, D3 and D4, type 2 serotoninergics (5-HT 2) and noradrenergic (alpha 1) receptors[27].

In some studies with clozapine, it has been observed that central serotonin remains unchanged[10] and other clinical studies and those in rats indicate that clozapine presents a sedative effect to which tolerance is produced, observing an increase of 5-H1AA in urine and CSF at ten days of treatment and in chronic treatments[28]. Ruch et al.[29] indicates that there is an increase of serotonin in the brain of rats treated with clozapine, which may explain the effects of clozapine on sleep.

Sarafoff et al.[30] describe an increase in noradrenaline the morning after the administration of the drug and other authors (Coward[31]) report that clozapine increases homovanillic acid and striatal dopamine levels, does not induce supersensitivity of striatal receptors, has intrinsic anticholinergic activity and performs alpha adrenergic, serotoninergic and histaminergic blocking activity.

Rebound insomnia immediately after discontinuing clozapine, which disappears after readministering treatment with clozapine, is described. This may be due to dopaminergic hypersensitivity or to a cholinergic rebound, that may indicate the participation of GABAergic and perhaps antiglutamatergic activity[32].

In regards to hormonal variations, clozapine does not increase prolactin plasma levels.

Lee JH et al.[34] studied hormonal variations during sleep, observing a lower level of GH and cortisol during the REM phase than in wakefulness stage in untreated schizophrenics. However, he observed that the administration of clozapine decreases the cortisol levels in the early treatment phase versus the maintenance phase and does not change the GH levels during all the treatment.

We ignore the possible role of clozapine on cytokines and sleep.

Clozapine and sleep parameters

In treatments with clozapine, sedation is defined as a usual side effect, however the studies published on the changes that it induces on sleep parameters are few and their results are inconsistent. The studies present deficiencies in their methodology, in many cases lacking baseline registries of sleep and of controls for clozapine induced fever, that alters nighttime sleep. Furthermore most are short term treatments.[33]

From the different studies, we can obtain the following data in humans:

- Increase in total amount of sleep[34].
- Increase in sleep efficiency[35].
- Improvement in sleep continuity[34,36].
- Increase in phase 2 sleep[34] versus phase 1[35].
- Increase of phase 1[37] according to some authors and reduction according to others[38].
- Reduction of deep slow wave sleep, basically phase 4[35,36].
- Increase of REM sleep at cost of slow wave sleep[36,39].
- Decrease of REM phase, without rebound phenomena during withdrawal[37].
- Increase of NREM sleep phase[35].
- Increase of REM sleep density, but not the total amount of REM35
- Dissociation of sleep mechanisms[36].

In studies with single dose clozapine injection in experimental animals, REM sleep is suppressed in a dose-dependent way, without changing the slow wave sleep. When clozapine is administered to the rats continually, it alters slow wave sleep, even strengthening it for three days after treatment. REM sleep decreases with tolerance phenomenon and without rebound[40]. In cats, Susic et al.[37] found a dramatic reduction in paradoxical sleep and slow wave sleep, that was maintained for 24 hours and was totally recovered.

Clozapine also increases circadian amplitude, perhaps through its high affinity for the dopaminergic D4 and serotoninergic 5-HT7 receptors in the suprachiasmatic nucleus[41,42].

CLINICAL CASE

We present the clinical case of a 24 year old male referred by his psychiatrist to our Sleep Unit to study daytime hypersomnia. He had been diagnosed of psychotic episode five years earlier, with absence of response to neuroleptics other than clozapine. The patient did not present positive symptoms, only having difficulties in social relationship, obsessive-like symptoms («Things get into my head and I can't get them out, such as a song, the need to count, etc.) and some concern for reading esoteric content («to look for meaning in my life»). No depressive type symptoms were observed.

He has severe hypersomnia that has become progressively worse in the last year, interfering in his quality of life significantly. The patient reports difficulty to main-

tain his alert level while performing routine and monotonous activities, concentration and attention difficulties, poor work performance and tiredness. He describes a possible episode of cataplexy that did not re-occur. He takes a nap and sleeps a mean of eight hours at night, without other accompanying psychopathological sleep phenomenon. The present dose and that of the last 3 years is 100 mg of clozapine.

In his pathobiography, no data having a biographic or development interest are recorded. He does not consume toxic agents.

Among his family background, the fact that his parents separated 14 years ago, and that his father died three years ago from pulmonary neoplasm stand out. The patient is the oldest of two siblings and his sister does not present psychopathology. An aunt of the patient receives treatment for a depressive type affective disorder.

Complementary examinations: general laboratory and thyroid hormone analyses within normal limits. Brain CT scan: within normal limits. Polysomnography: poorly structured sleep phases, with predominance of light sleep phases, decrease of deep sleep and absence of REM. Sleep latency very increased. Sporadic hypopneas and apneas. No desaturation. Sleep efficiency is 96.3 % (TST/SPT). Given the absence of REM, a second polysomnography was performed in which some REM sleep phases appeared, but it was very scarce and had very increased latency. Multiple latency test: the mean latency to sleep is 24 minutes and no REM sleep phase was recorded. Genotype: negative for DRB1, DQB1, DRB3/4/5.

Thus, organic causes of hypersomnia and also a possible narcolepsy were ruled out, treatment with psychodrugs (clozapine) remaining as a possible etiology.

Treatment was prescribed in the beginning with modafinil and then with methylphenidate without any observable clinical improvement and he did not tolerate the use of antidepressants (fluoxetine or chorimipramine) as possible potentiating therapy of wakefulness and muscular tone.

DISCUSSION

The patient presents a psychotic disorder, labeled as paranoid schizophrenia with obsessive like symptoms, that has only responded to clozapine. Among the sleep parameters that we have mentioned as typical of schizophrenia, the patient presents decrease in total sleep time, alteration in its continuity, predominance of light sleep with decrease of delta sleep (this reduction being potentiated by treatment with clozapine), however, as atypical symptoms, he presents absence of REM phase recorded on two polysomnographies performed without discontinuing treatment with clozapine (the absence of REM sleep cannot be attributed to the withdrawal of the neuroleptics). In schizophrenia, REM sleep increases (perhaps at the expense of slow wave sleep) and clozapine also potentiates the increase of the REM phase in humans.

In this case, no physical causes have been found that could explain either the absence of REM or the striking daytime hypersomnia, the administration of clozapine being the only factor related with these symptoms. Even though an increase in REM sleep in treatments with clozapine in humans is mentioned in the literature, there are authors such as Susic et al. who find a severe reduction of REM sleep in animals (cats) after administering clozapine in short periods.

Our case establishes a reflection on the role of clozapine on the REM sleep phase (potency?, does it decrease it?) as well as on the great variability in the results obtained in the investigation of sleep in schizophrenics, perhaps due to the need to contemplate many variables when a subject with psychosis is studied.

CONCLUSION

In spite of the recent advances in the study of sleep, of the consideration of this as a complex and active process, of the role that the clinical psychiatrists grant sleep disorders as key symptoms of alertness in the case of decompensations as well as the index of clinical improvement, we know very little about sleep in psychiatric disorders and the alterations that neuroleptics produce in it.

Our article aims to bring to mind the importance of sleep alterations in clinical psychiatry as well as the need to know the effects (not as well-known as those of benzodiazepines) that the commonly used drugs such as neuroleptics and, in our case, clozapine, have on it.

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