EFFECT OF THE ASSOCIATION OF AMANTADINE AND QUETIAPINE IN THE TREATMENT OF REM SLEEP BEHAVIOR DISORDER: CASE REPORT

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ABSTRACT: The aim was to report the case of a patient with REM sleep behavior disorder, unresponsive to standard treatment and with complete control of the condition after association of amantadine. Female patient, 45 years old, with systemic arterial hypertension and hypothyroidism, referred to neurological care, reporting frequent episodes of nocturnal agitation in the first hours of sleep, with walking and vocalization, waking up easily if called. She complains of drowsiness and anxiety, secondary to the impact of the RBD on her personal life. She mentions previous attempts at drug treatment with benzodiazepines (Bromazepam and Clonazepam), Zolpidem and Trazodone, all without clinical improvement, with Quetiapine being introduced at a low dose (not yet tried) 25mg, with a therapeutic target of 50mg with partial improvement only with 25mg. When trying 50mg, presenting a worsening of the picture. In a new follow-up, therapy with Amantadine 50 mg/day associated with Quetiapine 25 mg/day was started. The patient returned reporting a significant improvement in the condition, less frequent episodes associated with reduced nocturnal movement. After adaptation of the combined therapy, with adjustments in the dose of Amantadine, an increase of 50mg every 14 days up to 200 mg/day, with the possibility of using quetiapine 50mg (balance between the drugs), the patient evolved stable, with a great improvement in the quality of life and absence of new episodes of the sleep disorder.

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KEYWORDS: REM Sleep; Amantadine; Behavioral Disorder; Quetiapine.

EFEITO DA ASSOCIAÇÃO DE AMANTADINA E QUETIAPINA NO TRATAMENTO DO DISTÚRBIO DO COMPORTAMENTO DO SONO REM: RELATO DE CASO

RESUMO: O objetivo foi relatar o caso de uma paciente com transtorno comportamental do sono REM, sem resposta ao tratamento padrão e com completo controle do quadro após associação de amantadina. Paciente do sexo feminino, 45 anos, com hipertensão arterial sistêmica e hipotireoidismo, encaminhada a atendimento neurológico relatando episódios frequentes de agitação noturna nas primeiras horas de sono, com deambulo e vocalização, despertava facilmente se chamada. Queixa-se de sonolência e ansiedade, secundárias ao impacto do TCSREM em sua vida pessoal. Menciona tentativas prévias de tratamento medicamentoso com benzodiazepínicos (Bromazepam e Clonazepam), Zolpidem e Trazodona, todos sem melhora clínica, sendo introduzido Quetiapina em dose baixa (ainda não tentado) 25mg, com alvo terapêutico de 50mg com melhora parcial apenas com 25mg. Ao tentar 50mg, apresentando piora do quadro. Em novo retorno, iniciou-se terapia com Amantadina 50 mg/dia associada a Quetiapina 25 mg/dia. A paciente retornou referindo melhora significativa do quadro, episódios em menor frequência associados a redução na movimentação noturna. Após adaptação da terapia combinada, com ajustes da dose de Amantadina, aumento de 50mg a cada 14 dias até 200 mg/dia, sendo possível o uso da quetiapina 50mg (equilíbrio entre os fármacos) a paciente evoluiu estável, com grande melhora da qualidade de vida e ausência de novos episódios do distúrbio de sono.
PALAVRAS-CHAVE: Sono REM; Amantadina; Transtorno Comportamental; Quetiapina.

EFECTO DE LA ASOCIACIÓN DE AMANTADINA Y QUETIAPINA EN EL TRATAMIENTO DEL TRASTORNO DEL COMPORTAMIENTO DEL SUEÑO REM: REPORTE DE UN CASO

RESUMEN: El objetivo fue reportar el caso de un paciente con trastorno de conducta del sueño REM, que no responde al tratamiento estándar y con un control completo de la condición después de la asociación de amantadina. Paciente femenina, de 45 años de edad, con hipertensión arterial sistémica e hipotiroidismo, referida a atención neurológica, reportando episodios frecuentes de agitación nocturna en las primeras horas de sueño, con marcha y vocalización, despertándose fácilmente si se le llama. Se queja de somnolencia y ansiedad, secundarias al impacto de la RBD en su vida personal. Menciona intentos previos de tratamiento farmacológico con benzodiazepinas (Bromazepam y Clonazepam), Zolpidem y Trazodona, todos sin mejoría clínica, con la introducción de quetiapina a una dosis baja (aún no probada) de 25mg, con un objetivo terapéutico de 50mg con mejoría parcial solo con 25mg. Al intentar 50mg, presentando un empeoramiento de la imagen. En un nuevo seguimiento se inició tratamiento con 50 mg/día de amantadina asociado a 25 mg/día de quetiapina. El paciente retornó reportando una mejoría significativa en la condición, episodios menos frecuentes asociados a reducción del movimiento nocturno. Después de la adaptación de la terapia combinada, con ajustes en la dosis de Amantadina, un aumento de 50mg cada 14 días hasta 200 mg/día, con la posibilidad de utilizar quetiapina 50mg (equilibrio entre los fármacos), el

paciente evolucionó estable, con una gran mejoría en la calidad de vida y ausencia de nuevos episodios del trastorno del sueño.
PALABRAS CLAVE: Sueño REM; Amantadina; Trastorno del Comportamiento; Quetiapina.

1. INTRODUCTION

The rapid eye movement sleep behavior disorder (RBD) is a parasomnia characterized by complex motor activity resulting from the loss of muscle atonia during rapid eye movement (REM) sleep (BOEVE et al., 2004). The condition is often associated with progressive neurodegenerative diseases such as Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) (GAGNON et al., 2002; BOEVE, 2010; MIGLIS et al., 2021; TOURINHO et al., 2023). Clinically, in these synucleinopathies, the RBD may emerge as a prodromal symptom capable of preceding, by decades, presence of cognitive deficits and/or motor disorders (BOEVE, 2010). The behavioral management of these patients involves modifying the sleep environment to prevent possible injuries resulting from the condition, as well as pharmacotherapy, in which the main drugs indicated are clonazepam and melatonin (AURORA et al., 2010; HOWELL et al., 2022; HOWELL et al., 2022).

The aim of this report is to describe and discuss a case of a patient with RBD unresponsive to standard treatment, but with complete improvement of the symptoms after the pharmacotherapy of amantadine and quetiapine. Clinical data were collected from the patient's electronic medical record and discussed according to the literature review about RBD. This work followed the principles of the Helsinki Convention and its subsequent amendments, as well as the regulatory guidelines and norms for research involving human beings, defined in Resolutions nº 466/2012 and 510/2016 of the National Health Council/National Research Ethics Committee (CNS/CONEP).

2. CASE REPORT

In March 2020, a 45 years old female patient, single and residing in a city in the interior of Paraná, with systemic arterial hypertension and hypothyroidism, was referred to neurological care reporting, by her mother with whom she lived, frequent episodes of agitation during sleep, with walking, vocalization and easy awakening when called. The patient complained of drowsiness and anxiety, probably secondary to the RBD, which impact negatively on daily activities. She reported an increase in the frequency of

episodes, going from weekly to daily, since infection with SARS-CoV-2 one year ago. Due to the lack of improvement with previous therapies, with the use of diazepam, clonazepam, trazodone and zolpidem, she was not using medication for this condition. *Personal history*: similar episodes of nocturnal restlessness in childhood, with complete improvement in adolescence and return when adult. *Familiar history*: an uncle with epilepsy**.** *Medications in use*: losartan, propranolol, hydrochlorothiazide, levothyroxine and combined oral contraceptive composed of cyproterone and ethinylestradiol. On physical examination, there was a slight decrease in Right Upper Limb Balance (RULB) and absence of alterations in the other topics of the neurological examination.

After medical evaluation, pharmacotherapy was started with clonazepam 25 mg/mL. The initial dose of 4 drops was prescribed at night, at bedtime, with a gradual increase of 1 drop/day up to a maximum dose of 10 drops. Due to the findings of the physical examination, doppler ultrasonography of the mesencephalon with investigation of *Substantia Nigra* and Magnetic Resonance Imaging (MRI) of the Brain with investigation of nigrosome 1 and neuromelanin were requested. Regarding sleep complaints, a Polysomnography (PSG) was requested with Multiple Sleep Latency Test and an Electroencephalogram (EEG). It is important to point out that these exams were done and assessed at different times and with a long time between request and assessment.

At the seventh day of treatment, the patient returns with a normal EEG result (of good quality), but with a worsening of the clinical presentation where she reported vivid dreams and “horrible nightmares”. Due to absence of response to clonazepam, the benzodiazepine was replaced by quetiapine, at an initial dose of 25 mg/day, at bedtime, increased after the fifth day to 50 mg/day. There was partial improvement with 25 mg/day, but it worsened when the dose was increased to 50 mg/day.

Regarding the imaging exams, the Midbrain Doppler demonstrated bilateral reduction of the Substantia Nigra, with 15 mm^2 on the left side and 10 mm^2 on the right side (RV: > 25 mm^2). This result was compatible with the investigation of nigrosome 1 and neuromelanin, received only 15 months after the request, in which an absence of the swallow's tail signal was verified. On the other hand, the polysomnography, delivered 8 months after the request, presented no changes. It is important to highlight that the Multiple Sleep Latency Tests were not performed in the Polysomnography, suggesting impairment of the technical quality of the exam.

Considering the result of the Midbrain Doppler exam, the slightly decreased RULB, the poor response to quetiapine and the lack of response to previously used drugs, it was decided to modify the pharmacotherapy with the introduction of amantadine (50 mg/day) and a reduction in the dose quetiapine to 25 mg/day. After 14 days, the patient reported a significant improvement in the symptoms, with a reduction of 80% (SIC) in the frequency of episodes and nocturnal movement, remaining under this pharmacotherapeutic regimen for another 45 days to stabilize the treatment. Upon return, the patient reported continued clinical improvement with no impact on her daily activities, which led to maintenance of the drugs and their respective dosages. After 2 months, the patient reports having one or two crises/month, but with less intensity. Therefore, amantadine dosage was increased to 100 mg/day (50mg every 12 hours) with continuation of quetiapine at 25 mg/day. She remained well and stable for 6 months, when the episodes increased in frequency (3 to 4 every 14 days) but not in intensity. As a result, there was an increase in the dose of amantadine to 150mg/day (100mg/day and 50mg/night), with improved response to therapy. The scheme was maintained for one year, being evaluated every 60 days. Finally, with the result of the MRI, the dose of amantadine was increased to 200 mg/day (100mg every 12 hours) and the dose of quetiapine was maintained at 50mg at bedtime. The new pharmacological scheme promoted complete improvement of the condition that has remained stable for 2 years.

3. DISCUSSION

RBD was described for the first time in humans by Schenck et al., (1986), and it results from failure to inhibit spinal motor neurons during the REM sleep phase, with consequent loss of muscle atony in this sleep phase (AURORA et al., 2010). However, there are multiple possible causes, including structural damage, synucleinopathies and other neurodegenerative diseases, as well as orexin deficiency (narcolepsy) and toxic effects of medications.

The most common cause of idiopathic RBD is the presence of neurodegenerative disease related to alpha-synuclein (MIGLIS et al., 2021; MAHOWALD et al., 2007). There are several case reports and observational studies that reinforce this premise (AURORA et al., 2010; BOEVE et al., 2013; SCHENCK et al., 2013; OLSON et al., 2000; IRANZO et al., 2006). Boeve et al. (2004) identified, in a case series, that the RBD preceded, on average, 10 years the onset of cognitive impairment, parkinsonism or

autonomic dysfunction in 51% of patients, and 94% of such neurodegenerative disorders were synucleinopathies. In another study, Schenck et al. (1986) observed that 81% of patients initially diagnosed with RBD developed parkinsonism or dementia, on average, 14 years after the beginning of the sleep disorder. Oslon et al. (2000) noted neurological disorders in 57% of patients diagnosed with RBD, in which 86% of these disorders being Parkinson's disease (PD), dementia without parkinsonism, and multiple system atrophy (MSA). In addition, Iranzo et al. (2006) in a retrospective study, described that 45% of patients with RBD developed PD, dementia with Lewy bodies (DLB) or MSA in about 11 days after the onset of the sleep disorder.

Different studies point out that the RBD is present in a significant proportion of patients with MSA, DLB and PD. These researches aim to report the prevalence of RBD, that can vary between 70% (BOEVE et al., 2001) and 90% (PLAZZI et al., 1997) for patients with MSA, about 40% for patients with DLB and between 15% (GJERSTAD et al., 2008) and 33% (GAGNON et al., 2002) for patients with PD. For the development of neurodegenerative disease in patients with idiopathic RBD, a risk of 17.7% at 5 years, 40.6% at 10 years and 52.4% at 12 years is estimated (POSTUMA et al., 2009). RBD may be related to other neurological disorders, such as spinocerebellar ataxia, limbic encephalitis, multiple sclerosis, as well as different types of sleep disorders, such as narcolepsy (BONAKIS et al., 2008; NIGHTINGALE et al., 2005). Another important feature is the correlation with changes in neuronal circuits that originate in the pons and follow to spinal motor neurons. However, dysfunctions in anatomical areas such as the *locus coeruleus*, rostral pons, and dorsal midbrain demonstrate a significant correlation with RBD. As well as endogenous factors, exogenous factors can influence and trigger this disorder, through toxic effects to specific medications, such as tricyclic antidepressants, monoamine oxidase inhibitors, serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, beta-blockers and others (BOEVE et al., 2007).

For the effective diagnosis of the RBD, is made through clinical anamnesis associated with PSG. However, this test was unable to certify the expected alteration in this case. Considering the clinical findings, in order to complement the diagnosis, doppler ultrasound of the midbrain with a search for the *substantia nigra* and brain MRI with a search for nigrosome 1 and neuromelanin were performed. The results of those exams showed a significant reduction in the *substantia nigra*, raising the suspicion of a possible progression to DLB. It is important to point out that in situations in which PSG is difficult

to perform or in which it is difficult to apply a good technique and if, only if, clinical findings are observed, even if small but consistent with movement disorders, it is necessary to consider and evaluate complementarily the possibility of the presence of pathologies such as synucleinopathies.

In some cases, for diagnostic purposes, it is possible to initiate therapy for RBD associated with movement disorders in the primary phase (before movement disorders become significant) and in the secondary phase (symptomatic). Thus, the use of Amantadine, recommended for movement disorders, was effective both as a prevention for possible future manifestations and as a solution for the RBD.

From an anatomical point of view, different areas of the central nervous system (CNS) are involved in the various stages of sleep and wakefulness. The cortical activation necessary for maintaining wakefulness is guaranteed by an extensive network of subcortical structures and pathways, of which the hypothalamus plays a key role (NEVES et al., 2013; CARLEY and FARABI, 2016). In specific areas such as the anterior hypothalamus, there are GABAergic neurons, which stimulate and control NREM sleep by inhibiting the ascending activating reticular system and the basal forebrain. In conjunction with the lateral/posterior hypothalamus, these regions are responsible for maintaining sleep, while pontine nuclei promote REM sleep. Many substances that induce drowsiness act on GABA receptors, such as alcohol, sedative hypnotics, benzodiazepine agonists, and barbiturates. (KRYSTAL AND SORSCHER, 2016). Other neurotransmitters are involved with the alert system, including acetylcholine, dopamine, serotonin, noradrenaline and hypocretin/orexin (CHROVERTY, 2010).

The drug amantadine belongs to the class of antivirals, which for a long time was administered for the prophylaxis of influenza A. Its mechanism of action is linked to the inhibition of the M2 protein present in the virus membrane, which is very important for its entry and replication of the virus in the host cell. However, the mechanism of resistance developed by the use of this antiviral ended up rendering amantadine ineffective for the treatment of influenza (SHAMAILA et al., 2021; SWIERCZYNSKA et al., 2012). On the other hand, amantadine exerts other actions in the human body, being administered to help glutamatergic, dopaminergic, serotonergic, and noradrenergic neurotransmission. This possible therapeutic action has expanded the use of this drug in clinical practice. In a study carried out with mice, amantadine showed a mild competitive antagonistic action on NMDA receptors, and an inhibition of dopamine reuptake with increased expression

of D2 receptors. At higher doses used in the clinic, inhibition of serotonin and noradrenaline reuptake was observed (RAUPP-BARCARO et al., 2018; RAUPP-BARCARO et al., 2021). The therapeutic actions of amantadine on neurotransmission are significant which justifies its clinical use for neurodegenerative diseases such as Parkinson's Disease (PD), even in drug-induced parkinsonism, or with brain injury, or attention deficit hyperactivity disorder and also autism spectrum disorder (RAUPP-BARCARO et al., 2018; HEATHER and ROSS, 2020; LOGGINI et al., 2020).

Relating that REM sleep is generated and maintained by the interaction of neuronal pathways controlled by several neurotransmitters (such as glutamate, dopamine, acetylcholine, histamine, orexin and hypocretin) and that the glutamatergic pathway involves neurons of the locus coeruleus that activates during REM sleep and exerts the function of regulating some of its characteristics such as muscle paralysis, it is necessary, in this case, to evaluate the action of this atony that begins when the neurons of the locus coeruleus activate, through NMDA receptors, GABAergic neurons of the ventromedial medulla, which inhibit skeletal motor neurons (FRAIGNE et al., 2015). Although little studied, the dopaminergic pathway also participates in the regulation of the sleep-wake cycle, being activated during wakefulness and inhibited during sleep. In both cases, the pattern of depolarization of dopaminergic neurons is similar. However, regarding REM sleep, there is a higher frequency of triggers (LENA et al., 2005). It is interesting to highlight that the administration of dopamine in dopaminergic neurons of the locus coeruleus inhibits REM sleep or produces REM sleep without atonia (SAKAI, 1991).

This involvement of dopaminergic pathways in the control of REM sleep suggests changes in the sleep-wake cycle in patients with impaired dopaminergic transmission, such as PD patients. Studies show that patients with PD have greater motor activity during REM sleep (ZOETMULDER et al., 2016). Considering a systematic review of 67 studies, including 63 meta-analyses of patients with PD undergoing polysomnography, the results demonstrated a significant reduction in REM sleep time in the group of patients with PD (SEPPI et al., 2019; ZHANG et al., 2020).

Although the exact mechanisms of REM sleep control by dopamine are still not fully understood, it is possible to suggest that dopamine exerts an inhibitory effect on muscle atony in patients without changes in dopaminergic pathways. However, in situations where there is a reduction in the central levels of this neurotransmitter, as in PD, an increase in dopaminergic activity in the locus coeruleus could restore the

necessary balance to guarantee muscle paralysis during REM sleep. This action would justify the therapeutic effect of amantadine in the treatment of RBD observed in this report, mainly due to the fact that this drug increases dopaminergic transmission.

Furthermore, it is important to point out that increasing the dose of quetiapine triggered a worsening of the patient's clinical condition. Quetiapine is an atypical antipsychotic drug with sedative action at low doses (up to 50 mg/day), due to the blockade of histamine H1 receptors. However, at higher doses (800 mg/day), quetiapine has a D2 receptor blocking action (STAHL, 2021).

Therefore, it is possible to suggest that the RBD presented by the patient is due to the reduction of dopaminergic transmission, being corrected by the positive dopaminergic activity of the drug amantadine and aggravated by the anti-dopaminergic activity of the drug quetiapine in doses greater than 50 mg.

4. CONCLUSION

Based on sleep disorders such as RDB associated with diseases such as PD, DLB, and others that may have motor or non-motor manifestations, this study proposes to pay special attention to non-motor disorders. This allows hypothesizing the presence of an incipient movement disorder, anticipating a diagnosis even in the absence of very pronounced motor symptoms. It is important to emphasize that not every sleep disorder requires polysomnography as a complementary examination, such as parasomnias, for which the physician can request more additional tests by taking an investigative clinical history.

This report is of great relevance in medicine for presenting two innovative diagnostic therapies. First, in relation to an assertive diagnosis of a highly impactful disorder in the individual's daily life and, in view of the clinical anamnesis, it was necessary to seek other forms of complementary diagnosis. This process reaffirms the importance of meticulous clinical investigation, which allows new horizons of diagnostic research, with innovative and unusual strategies in clinical protocols, however no less significant, mainly in the inclusion of complementary exams, as mentioned in this case, which allows a more assertive diagnosis and favorable treatment. The second mention is related to associated therapy. In cases similar to this one, in which the patient does not respond to traditional therapies, the clinician must devise therapeutic strategies in order to allow investigations of other syndromes that, many times, may seem secondary

characteristics to the patient's main complaints, but which can trigger significant therapeutic responses. It is concluded, with this case, that the participation of the patient in the anamnesis and in the evolution of the condition, following the precepts of a good clinical history, it is necessary to review the clinical examination several times, with an innovative look, based on concepts fundamental aspects of pathophysiology, anatomy and pharmacology, which allows us to develop effective therapeutic strategies to the point of reducing drug therapy aimed at two or more syndromes and also a more assertive and favorable diagnosis, based on logical reasoning.

Therefore, movement disorders may be suspected in patients with idiopathic RBD unresponsive to clonazepam. In this case, replacement of this drug by amantadine is a possible therapeutic option.

STUDY LIMITATIONS

The present study had important limitations, since it reported a therapeutic response of a single individual in outpatient follow-up. In addition, other aspects such as control group and placebo were not applicable to the model of this study.

RECOMMENDATIONS FOR FUTURE STUDIES

In order to evaluate the therapeutic efficacy of this treatment for general population, other study models should be conducted, such as randomized clinical trials with a larger number of participants and considering other variables, such as placebo-controlled groups.

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