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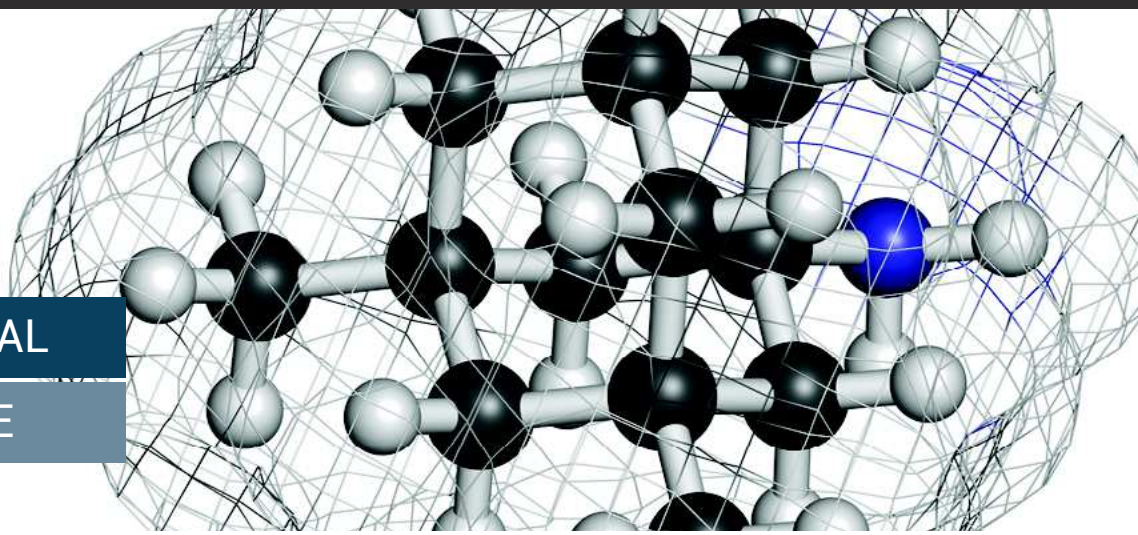

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MANIFORM EPISODE RELATED TO MEMANTINE THERAPY: UNRAVELING OF AN UNKNOWN ADVERSE SIDE EFFECT?

EPISODIO MANIFORME RELACIONADO CON TERAPIA CON MEMANTINA: ¿DESCUBRIENDO UN EFECTO SECUNDARIO ADVERSO DESCONOCIDO?

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ABSTRACT

Introduction: Memantine, a type of N-methyl-D-aspartate (NMDA) antagonist, is a drug approved by Food and Drug Administration to the treatment of moderate-to-severe Alzheimer disease (AD). Glutamate has been hypothesized to be released in excess in AD, perhaps in part triggered by neurotoxic amyloid plaques and neurofibrillary tangles. Memantine reduces abnormal activation of glutamate neurotransmission and thus interferes with the pathophysiology of AD, improves cognitive function, and slows the rate of decline over time.

Methods: Case report description based on the consultation of the patient's clinical records suggesting a new adverse side-effect associated with memantine taking. We performed a non-systematic review of the literature on the possible mechanisms that may be behind the development of this secondary effect and investigate the possible existence of other similar cases described in the literature.

Case Report: We present a case report of a 78-year-old female who developed maniform symptomatology after initiating memantine therapy. The symptomatology disappeared completely after the suspension of the drug, remaining psychopathologically stable at 12-months follow-up. This clinical report unravels a new possible adverse side effect of memantine, which is the triggering of maniform episodes.

Discussion: To the author´s knowledge there is only one more case report of a manic episode memantine-related published in the scientific literature, something that was not previously reported by the drug manufacturer.

Memantine appears to have some antidepressant properties and a few mechanisms which might contribute to the antidepressant-like effect of memantine have been proposed. Thus, as with antidepressants, a hyperbolic response to the drug may have the adverse effect of triggering maniform states.

Conclusions: Memantine should be adequately prescribed and symptoms suggestive of mood elevation must be explored in patients taking this drug. We also highlight that memantine should be used with caution in combination with antidepressants, especially in patients with a history of maniform / manic episodes. Lastly, we underline the importance of the rational and correct use of psychopharmacological therapy, namely the discouragement of the off-label use of drugs, which exposes the patients to unnecessary risks.

Keywords: Geriatric Psychiatry; Dementia; Clinical Pharmacology; Drug Side Effect; Memantine; Maniform episode.

RESUMEN

Introducción: La memantina, un tipo de antagonista de N-metil-D-aspartato (NMDA), es un medicamento aprobado por la *US Food and Drug Administration* para el tratamiento de la enfermedad de Alzheimer (EA) moderada o grave. Se ha planteado la hipótesis de que el glutamato se libera en exceso en la EA, liberado en parte por las placas amiloides neurotóxicas y los ovillos neurofibrilares. La memantina reduce la activación anormal de la neurotransmisión de glutamato y, por lo tanto, interfiere con la fisiopatología de la EA, mejora la función cognitiva y disminuye el deterioro progresivo.

Métodos: Descripción de un caso clínico sobre el cual, mediante los registros clínicos del paciente, se describe un nuevo posible efecto secundario asociado con la toma de memantina. Se realizó una revisión bibliográfica no sistemática sobre posibles mecanismos etiopatogénicos del desarrollo de este efecto secundario e investigamos la posible existencia de otros casos similares descritos en la literatura.

Caso Clínico: Mujer de 78 años que desarrolla sintomatología maniforme después de iniciar el tratamiento con memantina. La sintomatología remite completamente después de la suspensión del fármaco, permaneciendo estable psicopatológicamente tras 12 meses de seguimiento. Este caso clínico apunta a la existencia de un posible efecto secundario desconocido de la memantina, que es el desencadenar de episodios maniformes.

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Discusión: Hasta el momento, acorde con el conocimiento actual, sólo se ha descrito otro caso clínico en la literatura donde un paciente, tras la toma de memantina, desarrolló un episodio maníaco, efecto que los responsables del medicamento no han descrito.

La memantina parece contener propiedades antidepresivas, y se han descrito mecanismos explicativos que podrían contribuir a tal efecto antidepresivo. Así, tal como ocurre con los medicamentos antidepresivos, una respuesta exacerbada al fármaco puede generar efectos adversos como estados maniformes.

Conclusión: La memantina debe ser prescrita de forma adecuada y el estado de ánimo de los pacientes que toman este fármaco debe ser vigilado. Se recomienda que este fármaco se utilice con precaución en combinación con antidepresivos, especialmente en pacientes con antecedentes de episodios maniformes o maníacos. Por último, se enfatiza la importancia de un uso adecuado de los psicofármacos, particularmente evitando el uso off-label de medicamentos, que expone a los pacientes a riesgos innecesarios.

Palabras clave: Psiquiatría geriátrica; Demencia; Farmacología Clínica; Efectos secundarios de fármacos; Memantina; Episodio maniforme.

INTRODUCTION

Memantine, a type of N-methyl-D-aspartate (NMDA) antagonist, is a drug approved by Food and Drug Administration for the treatment of moderate-to-severe Alzheimer disease (AD) (Stahl, 2017). Glutamate has been hypothesized to be released in excess in AD, perhaps in part triggered by neurotoxic amyloid plaques and neurofibrillary tangles. This could interfere with the finetuning of glutamate neurotransmission, and possibly interfere with memory and learning. As the disease progresses, glutamate release could be increased to a level that is tonically bombarding the postsynaptic receptor, eventually resulting in excitotoxic cell death. Therefore, memantine reduces abnormal activation of glutamate neurotransmission and thus interferes with the pathophysiology of AD, improves cognitive function, and slows the rate of decline over time (Stahl, 2013).

Memantine, like other drugs for dementia, may slow progression of disease, but does

not reverse the degenerative process (Stahl, 2017).

The case report presented in this paper unravels a new possible adverse side effect of memantine, which is the triggering of maniform episodes.

METHODS

Case report description based on the consultation of the patient's clinical records suggesting a new adverse side-effect associated with memantine. Non-systematic review of the literature on possible mechanisms that may be at its origin and investigation of the existence of reports of other similar cases.

CASE REPORT

78-year-old female, widow for 33 years, with 14 sons and daughters. She was illiterate, retired, independent in all her activities and was living with one of her daughters.

She had a psychiatric history of recurrent major depression, first episode with 21 years of age, and several posterior to that date. Medicated for 10 years with escitalopram 10mg/day and lorazepam 1mg at bedtime, having been clinically stabilized for a long time. The patient also presented a medical history of bilateral neurosensorial deafness, with bilateral hearing aid.

She was observed in neurology consultation in June 2017 due to complaints of recent memory loss perceived by family members. The patient had episodes of forgetfulness for recent facts but could sometimes recover some memories with clues. She could go out alone without getting lost but would rather go out accompanied since she felt more secure. The family described behavior alterations (for example, getting up in the middle of the night to cook), that seemed to happen in the context of episodes of temporal disorientation. The patient did not have mood changes that raise suspicion of depressive pseudodementia, or other mood or behavior alterations that could raise suspicion of other mental illness.

She was independent for her everyday activities despite the evidence of modest cognitive decline from a previous level of performance. Her Mini Mental State Examination (MMSE) at that time was 22 out of 30. Thus, it was not possible to clinically diagnose dementia, and the complaints were more likely to be inserted in the context of mild neurocognitive disorder. Despite that, she was controversially medicated with memantine 20mg/day for the suspicion of onset of dementia syndrome without further investigation of the possible etiology.

Five months later, on November 2017, she was taken by relatives to the psychiatric emergency room for worsening of behavior changes that had started with the initiation of memantine therapy. The patient said that she "was feeling better than ever" and that "was cured". She described raised levels of energy and decreased need for sleep, waking up early in the morning to do many domestic activities (increase in goal-directed activity). Her family described elevated mood, with unusual jocose speech, which sometimes became irritable when contradicted. In this context she had expelled her daughter from her house.

Excessive spending was also evident with unnecessary purchases and exaggerated offers. She had a clear alteration in her functioning, which her family underlined had begun after the initiation of memantine taking. They denied previous similar episodes.

At objective mental examination she was vigil, calm, but uncooperative. Temporally sub-oriented, but oriented in space, person and situation. With elevated mood and tendency to irritability when contradicted. With pressured speech, but without flight of ideas. Evident subjective experience of excessive well-being and inflexible attitude towards the plans she had in her mind, even if the family considered them weird or improper. Without sensoperceptive changes. Insight regarding her psychopatological state was absent. Since the patient presented symptoms compatible with maniform state, psychiatric hospitalization for psychopathological stabilization and case study was proposed, which the patient accepted with reluctance.

During hospitalization memantine and escitalopram were discontinued, and risperidone 2mg/day was introduced, as well as oxazepam 15mg 3 times a day.

Cranial CT scan showed a mild leukoencephalopathy pattern of the head-to-body transition of left caudate nucleus, of probable ischemic nature.

Laboratory examinations were also performed (full blood count; glucose; ionogram; thyroid, renal and hepatic function; blood levels of calcium, phosphorus, magnesium, folic acid, and B12 vitamin; infectious serologies for B and C hepatitis, syphilis and HIV; urinalysis) and were all within the normal reference ranges.

On the MMSE the patient now scored 20/30 (still normal according to her schooling).

During hospitalization risperidone was titrated to 5mg/day, with progressive clinical improvement. The patient was discharged after 24 days, with the diagnosis of possible iatrogenic maniform episode due to memantine therapy, according to Naranjo's method for estimating the probability of adverse drug reactions (Naranjo, 1981). It was considered unlikely that the mood changes were due to antidepressive therapy, since it was a drug that the patient had already been taking at that dosage for 10 years, without any adverse effect.

At 12-month follow-up the maniform symptomatology did not recur, even with the progressive discontinuation of antipsychotic medication. For complaints of depressive symptoms, she was medicated for a period with escitalopram 10mg, with no recurrence of maniform symptoms even in the absence of mood stabilizing therapy.

However, the patient showed progressive memory loss specially for recent facts and a more prominent cognitive decline, with increasing interference on everyday tasks. That clinical development made possible to make the diagnosis of major neurocognitive disorder of probable vascular etiology since she had some alterations on the cranial CT scan of probable ischemic nature. The patient was then medicated with donepezil 10mg/day, which she has been taking for 7 months with good tolerance and without the recurrence of another maniform state.

DISCUSSION

To the author´s knowledge there is only one more case report of a manic episode memantine-related (Duan, 2018). The patient described by this author was also an elderly lady who had a psychiatric history of recurrent major depression and was diagnosed with a vascular neurocognitive disorder which justified the prescription of memantine. However, unlike the patient described by us, she presented more mood alterations and emotional instability prior to the maniform episode attributed to memantine taking, which could cons-

titute a fragility in this patient. She also had been diagnosed with depressive syndrome caused by cerebral infarction and atrial fibrillation four years earlier, while the patient described in this paper had no major vascular events, although she presented a mild leukoencephalopathy pattern of probable ischemic nature on CT scan. Unlike the patient we described, she was diagnosed with vascular neurocognitive disorder on the same admission she developed the maniform episode, while our patient was diagnosed later, which allows to exclude emotional lability associated with the neurocognitive disorder.

In this case report, the most likely diagnosis considered was maniform episode secondary to memantine taking. However, could also be contemplated as differential diagnosis: bipolar disorder with a late first maniform episode in a woman with a psychiatric history of recurrent major depression; the effect of antidepressant therapy; and neuropsychiatric symptoms in the prodromal stages of dementia. Nonetheless, the chronology of events points more towards the maniform episode have been a result of memantine therapy. Moreover, in 12 months, the maniform symptomatology did not recur, even with the progressive discontinuation of antipsychotic medication. Also, escitalopram 10mg was used without the recurrence of maniform symptoms even in the absence of mood stabilizing therapy, which makes the hypothesis of bipolar disorder or antidepressant iatrogenesis unlikely. The fact that the patient no longer exhibited behavioral changes despite the progression of cognitive decline also undermines the diagnosis of behavioral changes in the context of the onset of dementia syndrome, although it can´t be excluded. It can be hypothesized, however, that these fragility factors in the patient's medical history may have contributed, in addition to memantine taking, to the development of the maniform episode.

There is a recent accumulation of evidence regarding the therapeutic potential of memantine in the treatment of various psychiatric syndromes that may reflect the involvement of glutamate pathways in multiple psychiatric disorders (Lu, 2018). A large body of preclinical evidence has implicated the glutamatergic system in the pathophysiology of mood disorders, including the antidepressant effects of NMDA receptor antagonists in animal models (Sousa, 2017). Human studies have shown that the glutamatergic modulator ketamine effectively reduces depressive symptoms in individuals with major depressive disorder (MDD) or bipolar disorder, including treatment-resistant patients (Sousa, 2017). Clinical trials on the efficacy of memantine as an antidepressant agent in treatment of patients with MDD have reported mixed evidence, that could be justified by differences in patients' characteristics or exclusion criteria and different study designs (Amidfar, 2018). Some findings also suggest that the combined treatment of memantine with traditional antidepressants may induce an increased antidepressant effect (in a synergistic manner) than treatment with antidepressants alone (Amidfar, 2018). Moreover, based on uncontrolled observations and case reports, memantine seemed to also have potential anti-manic and mood stabilizing effects, however the evidence is conflicting (Veronese, 2016; Zheng, 2019).

Some mechanisms which might contribute to the antidepressant-like effect of memantine have been proposed, for example the antagonistic activity of memantine at NMDA receptor; changes in CREB, PKA, MAPK/ERK and CaMKII signaling pathways; interaction with neurotransmitter and receptor systems involved in depression (reuptake inhibition of serotonin and dopamine, antagonistic effects at 5-HT3 receptors, stimulation of cholinergic muscarinic receptors and effects on sigma receptor); among others (Amidfar, 2018). Thus, as with antidepressants, a hyperbolic response to the drug may have the adverse effect of triggering maniform episodes.

CONCLUSIONS

Since this is at least the second similar case described in the literature, it should be hypothesized that memantine may have the adverse effect of triggering maniform episodes, something that was not previously reported by the drug manufacturer.

Notwithstanding, more exploration needs to be done on the role of memantine in mood disorders, as its role from research so far seems to be conflicting, despite the scientific data on its hypothetical anti-manic and mood stabilizing effects.

Thus, we appeal to the adequate prescription of this drug and active research of symptoms suggestive of mood elevation in patients taking memantine. Despite this, it is also important to investigate the existence of a clear relationship between the appearance of maniform symptoms and memantine use, since psychotic symptoms and psychomotor agitation may occur in dementia syndromes, especially in later stages of the disease, when the use of memantine is

approved. We also suggest that memantine should be used with caution in combination with antidepressants, especially in patients with a history of maniform / manic episodes, as they have an increased risk of developing another of those events. Lastly, we underline the importance of the rational and correct use of psychopharmacological therapy, namely discouraging the off-label use of drugs which exposes the patients to unnecessary risks.

DECLARATION OF AUTHORSHIP, GOOD PRACTICES AND ASSIGNMENT OF RIGHTS

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Contribution: CC was responsible for review of the literature, manuscript design and writing. JM was responsible for the review and correction of all the content of the present work. Both authors approved the final version of the manuscript and are responsible for all its aspects.

Conflicting Interests: The authors declare the absence of potential conflicts of interest.

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