Psychosis Induced by the Interaction of Memantine and Amantadine: Lending Evidence to the Glutamatergic Theory of Schizophrenia

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Abstract

The dopamine hypothesis of schizophrenia is an enduring theory purporting that overactivity of the dopamine system is part of the pathogenesis of this illness. This theory is supported, in part, by the fact that amphetamines, via their enhancement of dopaminergic neurotransmission, can induce psychosis. More recently, aided by the psychoticomimetic effects of N-methyl-D-aspartate (NMDA) antagonists, it seems that glutamate, as well, has a role in the pathogenesis of schizophrenia (1). We present a case of psychosis possibly precipitated by the pharmacodynamic interaction of two NMDA antagonists.

Key Words: Glutamate, Psychosis, Brain Injury

Introduction

Psychosis, whether substance-induced or the result of psychiatric or medical illness, may present with hallucinations, delusions, and disorganized behavior. Our patient is a 58-year old motor vehicle accident victim with significant frontal-lobe deficits who became acutely psychotic following treatment with amantadine and memantine. Based on the glutamate model of psychosis, we propose that these non-competitive N-methyl-D-aspartate (NMDA) antagonists may have interacted to produce sufficient receptor hypofunction to elicit psychotomimetic effects. As such, the pharmacodynamic interaction between amantadine and memantine may help lend further support for the crucial role of glutamate in the complex pathogenesis of schizophrenia.

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Case Report

Our patient is a 58-year old African American male who was admitted to the trauma service at our teaching hospital after being struck as a pedestrian and rendered unconscious by a motor vehicle. Upon arrival in the trauma bay, he was found to be hemodynamically stable, but with a Glasgow Coma Scale (GCS) score of 12. He was subsequently intubated and treated for a left pneumothorax and for multiple fractures. Our patient was reported to suffer significant cognitive impairment as a result of his accident, but compound tomography (CT) scans of the head were unremarkable. This was treated as a coup-contrecoup injury, where it is not uncommon to sustain damage to the anterior-inferior surface of the frontal lobe (2). During the course of his hospitalization, our patient continued to have short-term memory defi-

cits, and he was unaware of any past medical or psychiatric history, prior medications, or family history. He denied drug and alcohol usage. Premorbid history was somewhat questionable, but per the social worker, he was fully functional and independent. His family refused to get involved with his recovery or provide collateral history.

The Psychiatry Consult/Liaison Service was asked to evaluate this patient's capacity to make medical and financial decisions. At that time he was found to have significant frontal lobe pathology such as impulsivity and inattention, as demonstrated by a positive Attention Screening Examination (ASE) with Letters, also known as the "Vigilant A" test. His working memory and short-term memory were poor, as he was unable to complete a three-digit-span in reverse or recall three objects. On a mental status exam (MSE), his affect was blunted, but he denied mood symptoms and perceptual disturbances. The patient's thought processes, however, were marked by a lack of goal-directed thinking and perseveration. Moreover, he displayed echopraxia and posturing. In response to the original intent of the evaluation, we found the patient lacked the capacity to make medical/financial decisions. The patient was immediately started on amantadine 100 mg PO BID and intramuscular (IM) olanzapine 2.5 mg at bedtime to treat symptoms of catatonia/frontal lobe syndrome (3) and akinesis (4), respectively. He was simultaneously started on memantine 5 mg PO daily and donepezil 5 mg PO daily in an attempt to stabilize his cognitive deficits. His orientation, short-term memory, attention, and symptoms of catatonia improved significantly over the following week, and amantadine was discontinued after six days. Nonetheless, donepezil was continued due to reported benefits in treating frontal lobe syndrome cognitive deficits (5). Magnetic Resonance Imaging (MRI) of the brain without contrast revealed two small, probably old, subdural hematomas, but these were considered insignificant by radiology. An electroencephalogram (EEG) one week later yielded a normal awake study with a posteriorly dominant 11 Hz alpha rhythm that was not consistent with delirium.

However, one day after amantadine was discontinued, our patient had an abrupt change of mental status that included agitation, disinhibition, and psychosis, with repetitive and stereotyped behavior, incoherence, auditory and visual hallucinations, grandiose delusions, and speech that was pressured and tangential. He scored 19/25 on the Bizarre Behavior subset and 31/45 on the Positive Formal Thought Disorder subset of the Scale for Assessment of Positive Symptoms (SAPS). SAPS is a 34-item scale on a 0-to-5 spectrum (0 = no abnormality; 5 = severe) designed to assess the positive symptoms of schizophrenia, but it is also useful for evaluating psychosis in other medical disorders. SAPS evaluates four domains of positive symptoms, including a five-question subset on Bizarre Behavior and a nine-question subset on Positive Formal Thought Disorder applicable to our patient; the other domains are Hallucinations and Delusions (6).

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In response, the patient was started on valproate 500 mg PO TID, and his olanzapine was increased to 10 mg IM daily to address his behavioral symptoms. Additionally, his memantine was stopped because the authors suspected a possible drug interaction with the previously discontinued amantadine as a causative agent for the development of these positive symptoms. Two days after stopping the memantine, our patient's positive symptoms had attenuated, and he tallied 8/25 and 14/45 on the two subsets of SAPS. The olanzapine was gradually titrated to 10 mg PO BID.

Shortly thereafter, the patient no longer demonstrated any type of psychosis or disorganized behavior. His affect remained bright and full-range, with spontaneous speech and a lack of perceptual or psychomotor abnormalities. Stereotypical behavior and catatonic posturing resolved. Moreover, the patient was oriented to person and place with minimal cues and was usually oriented to time. His cognitive deficits and frontal-lobe impairment remained, however, and are most likely sequelae of his traumatic brain injury. On discharge from the hospital, the patient was given a seven-day supply of olanzapine 10 mg BID. Unfortunately, he was lost to follow-up.

Discussion

A rapidly growing body of clinical and preclinical data is linking the NMDA receptor to human memory, attention, and other cognitive processes (7). As previously mentioned, noncompetitive NMDA receptor antagonists, such as phencyclidine (PCP), ketamine, and MK-801, can produce psychosis in humans (8). Moreover, progressive increases in the degree of NMDA receptor hypofunction within the brain produce an increasing range of cognitive and behavioral changes, beginning with deficits in free recall and recognition memory and leading to a clinical syndrome similar to schizophrenia. Sustained and severe NMDA receptor hypofunction can even lead to irreversible neurotoxicity. The mechanism underlying these drug-induced effects is postulated to involve the same general disinhibition process in

which NMDA antagonists eliminate gamma-amino-butyric acid (GABA)-ergic inhibition, leading to the simultaneous excessive release of acetylcholine and glutamate (9). Furthermore, given that pyramidal neurons in the prefrontal cortex are the principal source of cortical glutamate neurotransmission (10), NMDA hypofunction in this area, and its connections, may produce a pattern of dysregulation of dopamine systems that further destabilizes NMDA-mediated connectivity and plasticity (11).

While amantadine and memantine monotherapy are generally not associated with prominent psychotogenicity, their use in combination may produce sufficient NMDA receptor hypofunction to induce psychosis in a subset of patients, as may have been the case with our patient.

Amantadine and memantine are both NMDA receptor antagonists with neuroprotective properties and therapeutic potential in numerous central nervous system disorders. Memantine, a derivative of amantadine, is a low-to-moderate affinity, uncompetitive open-channel NMDA-receptor blocker which binds preferentially to the NMDA-receptor-operated cation channels (12). The drug's excellent safety and efficacy profiles are attributed to its moderate potency and rapid, strongly voltage-dependent blocking kinetic (9); however, there are case reports of memantine-induced psychoses (13). In contrast, amantadine causes the channel gate of NMDA receptors to close more quickly, and although the drug's binding inhibits current flow through the receptor channels, its main inhibitory action results from stabilization of the channel's closed states (14). Amantadine, therefore, is more of a "gating antagonist" than a true channel blocker. While amantadine and memantine monotherapy are generally not associated with prominent psychotogenicity, their use in combination may produce sufficient NMDA receptor hypofunction to induce psychosis in a subset of patients, as may have been the case with our patient. As mentioned, memantine, when compared to other NMDA antagonists, is considered to be of low-moderate potency while amantadine is considered a low-potency NMDA antagonist. Both memantine and amantadine bind to the same site, but the latter's significantly lower potency for the NMDA receptor seems to make it less likely to be a significant contributor to the formation of psychoses, if indeed these two NMDA antagonists did interact to produce psychoses (15). Regardless, it is difficult to predict whether this interaction would be synergistic or additive.

Conclusions

We feel this case report highlights two interesting possible neurobiological phenomena with regard to psychosis. First, as reported by Carroll et. al. (16), treatment with amantadine and/or memantine has resulted in attenuation of symptoms of catatonia. Since olanzapine was started simultaneously with amantadine and memantine, and there are case reports of successful treatment of catatonia with olanzapine (17), the resolution of catatonia in our patient could also be attributed, in part (or whole), to olanzapine. Even more fascinating, we feel this case lends support to the glutamate model in the pathogenesis of schizophrenia, which was sparked by reports of PCP and ketamine inducing positive and negative symptoms of schizophrenia. We present this case of memantine- and amantadine-induced psychosis as a novel means of studying the glutamate model of schizophrenia without utilizing the potent, and illegal, NMDA antagonists PCP and ketamine.

There are several limitations in our proposed theory of medication interaction causing our patient's psychoses. Either amantadine or memantine used in monotherapy could precipitate psychosis. According to the package insert for memantine, confusion and hallucinations are potential adverse effects, albeit not statistically significant versus placebo. Similarly, confusion and seizures can be seen with amantadine use, though these adverse effects usually only affect elderly patients and patients with renal disease (11). While valproate was added to treat aggressive symptomatology, it is also an NMDA antagonist that potentially could have accentuated psychoses if NMDA receptor antagonism was etiologically related to the development of our patient's psychoses (18). Furthermore, olanzapine was continued during the amantadine and memantine dechallenge period; thus, it is conceivable that the resolution of our patient's psychoses was due to the antipsychotic effect of olanzapine. In addition, given a lack of collateral history about our patient, we could not rule out premorbid schizophrenia as the cause of his psychoses. Finally, frontal cortical dysfunction has been reported to increase the risk of psychoses. In fMRI studies, vulnerability to psychosis was associated with medium-to-large effect sizes when prefrontal activation was contrasted with that in controls (19). Therefore, it is possible that our patient's psychoses could be attributed to the psychotomimetic effects of NMDA antagonism and frontal cortical dysfunction due to traumatic brain injury.

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