Visual hallucinations and agitation in Alzheimer's disease due to memantine: report of three cases

Memantine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is currently the only drug proposed for the treatment of moderate to severe Alzheimer's disease.[1] It has been shown to have neuroprotective effects by inhibiting the excitotoxic effect of NMDA glutamate receptors.[2] Memantine has a tolerability profile similar to placebo.[1] However, the worsening of psychotic symptoms in patients with Lewy body dementia (LBD) treated with memantine has been recently reported.[3] We describe three patients with probable Alzheimer's disease who developed worsening or de novo visual hallucinations and agitation after memantine treatment.

Case reports

Patient 1 was a 65-year-old woman with a 2-year history of slowly progressive cognitive decline, affecting episodic memory, naming and executive-attentive skills. Functional abilities of daily living were impaired. Physical and neurological examination, routine blood tests and electrocardiogram (ECG) were normal. Magnetic resonance imaging (MRI) of the brain showed a bilateral frontotemporal atrophy. A diagnosis of probable Alzheimer's disease was made, and she was treated initially with rivastigmine, then 2 years later with donepezil (10 mg/day) for a further 2 years. Because the patient's Mini Mental State Examination (MMSE) score was 14/30 at 69 years, she was prescribed a combination treatment with memantine. Her other drugs included vitamin E supplements, citalopram and quetiapine for mild agitation. One week after the starting of memantine (5 mg/day), agitation increased in frequency and severity and she developed florid visual hallucinations, described as ''small animals going around the room''. A neurological examination showed a mild bradykinesia. Blood test, ECG, chest *x* ray and brain MRI were unremarkable. Memantine was discontinued, and she experienced immediate reduction of agitation and disappearance of the visual hallucinations. At a follow-up visit 3 months later, no other adverse effects were seen.

Patient 2 was a 75-year-old woman with a 5-year history of depressive symptoms, followed by slowly progressive cognitive decline affecting episodic memory, naming, visuoconstructional and executive skills in the past 2 years. Functional abilities of daily living were impaired, and moderate anxiety and depressive symptoms were present. Physical and neurological examination, blood tests and ECG were normal. Brain MRI showed bilateral atrophy and mild periventricular white matter lesions. The patient's drugs included atorvastatin and bisphosphonate. She was diagnosed with probable Alzheimer's disease and treated with donepezil (10 mg/day) for 3 years. As her MMSE score was 12/30, she was prescribed a combination therapy with memantine. Other drugs included paroxetine, trazodone, folic acid, vitamin E supplements, atorvastatin and bisphosphonate. After taking three doses of memantine (5 mg/day), she developed florid visual hallucinations, described as ''people looking at her through the windows''. Blood test, ECG, chest *x* ray and brain MRI were unremarkable. A neurological examination showed mild bradykinesia and rigidity. Memantine was discontinued, and within 24 h her visual hallucinations completely resolved. After 1 week, with the consent of the patient and her daughter, memantine was resumed and the visual hallucinations returned. Memantine was again discontinued and the visual hallucinations rapidly resolved. Over the next 6 months, no recurrence of the visual hallucinations was reported.

Patient 3 was a 73-year-old woman with a 3-year history of slowly progressive cognitive decline affecting episodic memory, naming and visuoconstructional skills. There was a concomitant impairment of functional abilities of daily living, occasional incontinence and mild apathetic symptoms. Physical and neurological examination, blood tests and ECG were normal. Brain MRI showed bilateral frontotemporal atrophy. She was diagnosed with probable Alzheimer's disease and started on rivastigmine treatment with a modest response. After 6 months, she was switched to donepezil with similar results. After further 6 months, she was administered galantamine treatment (progressively titrated up to 24 mg/day). After 2 years, she developed mild agitation and visual hallucinations, described as ''people coming out of the television screen''. As her MMSE was 12/30, she was prescribed a combination treatment with memantine. Other drugs included paroxetine, quetiapine and vitamin E supplements. One week after the starting of memantine (5 mg/day), the agitation, and in particular the visual hallucinations, worsened, to such an extent that relatives had to take her to hospital. At admission, blood test, ECG, chest *x* ray and brain MRI were unremarkable. A neurological examination showed mild gait disturbances. Memantine was immediately stopped and, within 48 h, agitation and visual hallucinations improved considerably. At a follow-up visit 3 months later, she reported mild agitation and infrequent mild visual hallucinations.

Discussion

We report three cases with probable Alzheimer's disease who developed worsening or de novo visual hallucinations and agitation after memantine treatment. The strict temporal relationship between the use of the drug and the onset or worsening of the symptoms, and the resolution once treatment was discontinued, suggests a causal link between the two phenomena. This hypothesis is strengthened by the fact that we were able to verify the recurrence of visual hallucinations after memantine administrationin in patient 2.

None of the clinical trials of memantine in monotherapy or combination therapy with cholinesterase inhibitors in patients with Alzheimer's disease reported the development of visual hallucinations or agitation as adverse effects.[1] However, the worsening of psychotic symptoms, including visual hallucinations, as a result of memantine treatment in patients with LBD has been described recently.[3] Memantine is structurally similar to amantadine, an influenza drug used for the treatment of Parkinson's disease, which has been reported to cause visual hallucinations in patients with Parkinson's disease.[4] Both drugs bind with low affinity to the ion channel phencyclidine site at the NMDA receptor.[2] Phencyclidine, an NMDA receptor antagonist with high affinity, induces psychotomimetic effects, including hallucinations, agitation and delusions.[2] The relative rapid off-rate (that is, the time taken for a drug to vacate a receptor binding site) of memantine is crucially important for its clinical tolerability.[2] Some patients with Alzheimer's disease could be susceptible to concomitant neurotransmitter and receptor imbalance, as proposed to occur in patients with LBD.[3] However, in the absence of pathological confirmation, our patients may represent those subjects with Alzheimer's disease with concomitant LBD pathology.[5] Because of the fact that all three patients were also receiving antidepressant drugs of the selective serotonin reuptake inhibitor class, another possible explanation is that a drug interaction between memantine and the serotonin reuptake inhibitors might have occurred, which could have increased the potential for inducing or worsening hallucinations and agitation. Further studies or case reports are required regarding the incidence of these side effects and the underlying mechanisms of action before definitive conclusions can be reached.

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Hemimacropsia after medial temporo-occipital infarction

Dysmetropsia is a disorder of visual perception characterised by an apparent modification of the size of perceived objects.[1–3] Objects can appear larger (macropsia) or smaller (micropsia) than their actual size. Dysmetropsia can result from retinal oedema causing a dislocation of the receptor cells and from lesions affecting other parts of extracerebral visual pathways. Transient micropsia can also result from epileptic seizure, migraine, infectious mononucleosis, the action of mescaline and other hallucinogenic drugs, and psychopathological phenomena.

Permanent dysmetropsia following focal cerebral lesions is rare. Most of the prior reports described hemimicropsia due to lesions mainly involving the lateral aspect of the visual association cortex.[1–3] However, reports of hemimacropsia following focal cerebral lesions have been extremely rare[1 4] and hemimacropsia following a focal vascular lesion has not been