Olanzapine for delirium in parkinsonism: Therapeutic benefits in lieu of adverse consequences

Sir,

Drug-induced (dopaminomimetic) psychosis and confusional states (i.e. delirium) are found to occur frequently in parkinsonism.1 Delirium is generally managed by the withdrawal of anticholinergic and dopamine agonist drugs, individually or concomitantly.2 If necessary, antipsychotics are instituted in low doses.2 Atypical antipsychotics (clozapine, olanzapine) though reportedly useful, are associated with delirium or confusion as an adverse effect due to intrinsic anticholinergic properties,3 mediated through muscarinic M1 receptors in the brain.4

A 31-year-old woman presented with history of obstructive hydrocephalus (due to aqueductal stenosis) 2-1/2 years back, which was successfully managed with a ventriculo-peritoneal shunt. There was a recurrence of symptoms, associated with delirium, about 1 year back. This was followed by the appearance of extrapyramidal symptoms in the form of bradykinesia, rigidity, and tremors. A diagnosis of post-anoxic parkinsonism was made. She was treated with a combination of 25/100 mg levodopa/carbidopa half tablet three times daily, and trihexyphenidyl 2 mg once daily. She improved but developed withdrawal and retarded behavior one month prior to our evaluation. Imipramine (a tricyclic antidepressant) 25 mg three times daily was added by an external agency, but this led to worsening of symptoms. On psychiatric evaluation she was found to be in delirium, diagnosed as per DSM-IV criteria, for a period of 2 weeks. She was initially managed by stoppage of all drugs except levodopa/carbidopa (25/100 mg), which was reduced from four tablets to half tablet three times daily. No clinical change in delirium with worsening of parkinsonism features (gross tremors leading to inability to swallow and sit or walk unsupported) necessitated hike in dose of levodopa/carbidopa (25/100 mg) to three times daily. Haloperidol, a preferred drug for treating delirium,4 and other typical antipsychotics were not initiated as they could have worsened the parkinsonism features.5 Clozapine was not started due to lowered level of consciousness and drooling of saliva secondarily to the clinical diagnosis; these could have worsened due to the side-effect profile of clozapine. Risperidone (an atypical antipsychotic) could not be tolerated as, on initiation, at 1 mg/day there was marked drowsiness and increase in rigidity. Low-dose olanzapine (initiation dose = 1.25 mg once daily, maximum dose = 3.75 mg once daily), gradually titrated, led to resolution of delirium with no further worsening of motor symptoms over a three-week period. The patient thereafter maintained this delirium-free state over a follow-up period of eight weeks. During this time, no increased motor symptomatology was reported and none was detected on examination. Dopaminergic medications were not decreased. Thereafter, olanzapine was discontinued and she has maintained well for a period of twelve months.

Literature till date has mentioned the efficacy of olanzapine in treating dopaminomimetic psychosis, simultaneously cautioning about delirium1,5 and worsening of parkinsonism6,7 as its side-effects. Our patient did not develop worsening of motor symptomatology during treatment with olanzapine, a response that was maintained on follow-up too. The delirium also responded favorably.

Olanzapine demonstrates significant antagonism of serotonergic 5HT3 receptors leading to potentially cognitive-enhancing effects.3 It is also associated with differential antagonism of dopaminergic, histaminergic, cholinergic and serotonergic receptors in the brain. This differential antagonism of M1 and 5HT3 receptors could possibly explain the observed beneficial effect rather than a deleterious effect on the delirium in our case. To the best of our knowledge, this is the first case report in which olanzapine has been successfully used to treat delirium, an otherwise documented side-effect of the same.8 This patient’s experience also illustrates that failure of one atypical neuroleptic does not preclude success with a second atypical neuroleptic. Further studies are warranted to understand the biological basis of this therapeutic response so as to establish the potential of olanzapine as a possible useful agent for managing psychotic and confusional states in patients with parkinsonism.

References

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Recurrent cerebral venous and peripheral arterial thrombosis

Sir,

Hereditary thrombophilia is caused by a variety of inherited disorders, which result in a familial tendency to recurrent thrombosis usually manifesting at an early age. Patients generally present with venous thrombosis, and arterial thrombosis if present, is most often due to atherosclerosis. However, in young individuals with arterial thrombosis, lacking recognized risk factors for atherosclerosis, studies have shown the prevalence of a hypercoagulable state to be 12 to 40% (low levels of Protein C, Protein S, or antithrombin III, or the presence of lupus anticoagulant).1 The occurrence of a venous and an arterial thrombosis simultaneously is an uncommon event, even in the presence of an underlying prothrombotic state. We present an unusual case of a young girl who presented with arterial and then venous thrombosis.

A 16-year-old girl presented to the emergency room of our hospital with a 3-day history of severe headache, vomiting and progressive visual loss. At the age of 14, she had developed a non-healing ulcer on her right foot, and three months later developed claudication of both lower limbs. She was evaluated for the same at another hospital and was found to have bilateral femoral artery thrombosis. She initially underwent a thrombectomy and ilio-femoral bypass, but subsequently developed gangrene and underwent bilateral above knee amputations. She was started on unfractionated heparin, but developed cavernous sinus thrombosis while on treatment, which resolved with higher doses of heparin. A complete thrombotic work-up was not done at that time but the bleeding time and the platelet count were normal. She was discharged from the hospital on oral anticoagulants and subsequently attended a rehabilitation clinic where limb prostheses were fitted. Anticoagulation was discontinued after six months and she was put on aspirin. She remained well for over a year until she developed her present symptoms.

At presentation, she was afebrile, irritable and uncooperative, had bilateral papilledema with no lateralizing or meningeal signs. A contrast enhanced CT scan of the brain revealed evidence of dural sinus thrombosis with bilateral parieto-occipital hypo densities (Figure 1). Magnetic resonance venography confirmed the presence of sagittal and transverse sinus thrombosis (Figures 2a and 2b).

Baseline coagulation profile was normal and she was started on unfractionated heparin infusion and anti-edema measures. Despite being on heparin, she worsened over the next two days and developed bilateral proptosis and chemosis suggestive of cavernous sinus thrombosis. Her activated partial thromboplastin time was not prolonged even with 20 units of heparin per kilogram body weight, per hour. The possibility of antithrombin III deficiency was considered and she was started on low molecular weight heparin with which her symptoms and signs resolved rapidly over the next two days. She was subsequently started on oral anticoagulants and discharged.

Protein C, Protein S and antithrombin III could not be assessed before she was started on anticoagulants due to technical reasons. DNA analysis was negative for Factor V Leiden and prothrombin mutations, but she was found to be heterozygous for the methylenetetrahydrofolate reductase C667T mutation.

Patients with hereditary thrombophilia generally present with venous thrombosis. The occurrence of a venous and an

Reference


Letter to Editor

Figure 1: Plain CT scan showing a large hypodensity in the right parietal lobe. The superior sagittal sinus is relatively hyperdense.