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Acute Psychosis Associated with Levetiracetam in a Patient with Frontal Lobe Tumour

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Introduction

Levetiracetam is a second generation anti-epileptic drug with novel mechanism of action.[1] It is chemically unrelated to other antiepileptic drugs and is the α-ethyl analogue of the nootropic agent piracetam.[1] Its mechanism of action is unclear though it is postulated to bind to a presynaptic vesicle protein 2A (SV2A) that ultimately reduces the synaptic release of glutamate, impending conduction of epileptic action potentials across the synapse.[2] The United States Food and Drug Administration (FDA) approved levetiracetam in 1999 as an adjuvant antiepileptic medication for partial seizures in adults.[3] Post marketing, open, uncontrolled clinical experience suggested potential benefit in patients with depressive symptoms with seizure disorder, bipolar disorder and premenstrual dysphoric disorder.[4]

Levetiracetam is of proven efficacy in epileptic patients with brain tumours, and, as it is also used as intravenous formulation, it can be used as loading dose for seizure prophylaxis during and early after craniotomy.[5] However, the category of behavioural symptoms including agitation, hostility, anxiety, apathy, emotional lability, depersonalization and depression was reported in 12.9% of patients on levetiracetam and psychotic symptoms was reported in 0.7% of patients.[4]

Case Description

26 year old male patient with headache, blurring of vision and seizures since 2years maintained on Phenytoin 100mg BD and Sodium valproate 500mg OD presented to Neurosurgery OPD. He was diagnosed with left frontoparietal high grade glioma and was admitted for craniotomy with gross total excision of tumour. Patient was started on intravenous Levetiracetam 500mg BD as seizure prophylaxis post craniotomy after withholding Phenytoin and sodium valproate. On postoperative day 4 patient developed behavioural abnormalities characterised by agitation, restlessness and decreased sleep and was referred for Psychiatry opinion. Patient had no past history

of mental illness and denied substance use. There was no family history of mental illness. On examination, patient was restless and unable to sit for longer than a few minutes. Speech was rapid and patient had intermittent visual hallucinations. He denied suicidality and paranoid ideation. Neurology opinion was taken and possibility of frontal lobe seizures ruled out. Delirium was ruled out as there was no fluctuation in sensorium. His blood investigations for electrolytes, renal function tests, liver function tests were within normal limits. Patient was initially started on Haloperidol which was discontinued the next day due to development of extrapyramidal symptoms. The medication was switched over to Quetiapine 50 mg BD but his symptoms worsened with appearance of manic features as grandiose religious delusions.

Considering the possibility of Levetiracetam induced psychosis, drug was withheld and the patient was started on Olanzapine 2.5mg BD orally later titrated to 5mg BD. He recovered from psychotic symptoms over next 48hours. Phenytoin 100mg BD and Sodium valproate 500mg OD was prescribed for seizure control.

The adverse drug reaction causality assessment was done using the Naranjo scale and it showed a possible association (score 4) of the reaction with Levetiracetam.[6]

Discussion

Levetiracetam is a pyrrolidine derivative that differs from all other currently approved antiepileptic medications in its chemical structure, pharmacological profile and mechanism of action, and as a consequence possess unique properties.[5] It is frequently used due to its ease of oral administration, excellent bioavailability and low rate of drug interactions as it is not metabolized by liver or bound significantly to serum proteins.[5] The need for laboratory monitoring is minimal when using levetiracetam.[5]

Levetiracetam is generally well tolerated but can cause somnolence, vomiting, anorexia, rhinitis, hostility, increased cough, rhinitis and otitis media.[5] Psychiatric and behavioural treatment emergent adverse events occurring in patients in decreasing order of incidence are hostility (11.9%), nervousness(9.9%), personality disorder (7.9%), emotional lability (5.9%) and agitation (5.9%).[5] Psychosis is infrequently associated with levetiracetam, occurring in approximately 0.7% of patients [5] but well described in multiple case reports.[1,2,3,7] Levetiracetam induced psychosis is reported to be common in patients with pre-existing psychotic disorder, patients on add-on therapy and rapid titration when there is an underlying neurological disease.[1]Levetiracetam induced psychosis is also reported to be common in children with prior cognitive deficits.[1]

Patients on Levetiracetam therapy with a frontal location of a brain tumour are at a higher risk, as compared to patients treated with other antiepileptic drugs, to develop Treatment Emergent Psychiatric Adverse Events (TE-PAE).[8] It can be hypothesized that levetiracetam interferes with specific frontal circuits, possibly already damaged by the tumour contributing to reduce further the activity of frontal lobe and to trigger TE-PAEs.[8]

Our patient underwent craniotomy with total excision of left frontal tumour. He did not have a past history or family history of mental illness. Symptoms were seen when levetiracetam was started at clinically permissible dose and at the onset of therapy. Based on the temporal sequence of events, neurology evaluation and negative diagnostic workup, the possibility of association of the drug and psychosis is high. Resolution of symptoms within 48hours of stopping levetiracetam further supports the hypothesis. Previous case reports demonstrated psychiatric adverse events with levetiracetam in epileptic patients with etiology other than brain tumours. Also behavioural problems was noticed on either increase in the drug dose or after 10days to 1 month of initiation of therapy.

In conclusion, given the increasingly widespread use of levetiracetam as seizure prophylaxis in head injury and brain tumours, clinicians should

consider close monitoring of patients for treatment emergent psychotic symptoms. Clinicians can be especially cautious of psychiatric adverse events of levetiracetam and consider the use of alternative antiepileptic medication while treating seizures in patients with frontal lobe tumour.

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