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Case Study

Drug-Drug Synergism: A Case of Risperidone-Valproic Acid Induced Parkinsonism

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ABSTRACT

Parkinsonism is a clinical syndrome characterised by tremor, bradykinesia, rigidity and postural instability. While commonly associated with idiopathic Parkinson's disease, drug-induced Parkinsonism is a notable adverse effect of certain medications, including antipsychotics like risperidone and antiepileptic drugs like valproic acid. The case report focuses on a 59-year-old female with schizophrenia and bipolar disorder who developed drug-induced parkinsonism after being treated with risperidone (4 mg/day) and valproic acid (290 mg/day). The patient presented with tremors, rigidity, bradykinesia, and a shuffling gait, symptoms resembling those of Parkinson's disease. A thorough evaluation confirmed the onset of parkinsonism, likely resulting from the synergistic interaction between the two medications. Risperidone is a second-generation antipsychotic used in the treatment of Schizophrenia, Bipolar Disorder, and irritability in autism disorder. Valproic acid is an antiepileptic drug used in the management of seizure and as a mood stabiliser. Risperidone, a dopamine D2 receptor antagonist, can reduce dopaminergic activity in the brain, leading to motor dysfunction. Valproic acid, while primarily used as an anticonvulsant and mood stabilizer, has been associated with an increased risk of extrapyramidal side effects. Concurrent use of these drugs may synergistically increase the risk of Parkinsonism, especially in elderly patients or those with comorbidities by altering the dopamine metabolism. After discontinuation of risperidone, the patient's symptoms improved significantly, with partial resolution of motor signs. However, mild residual tremor persisted, likely due to the lasting effects of valproic acid.

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The Patient Was Switched to An Alternative Antipsychotic with A Lower Risk of Extrapyramidal Symptoms, And Her Condition Stabilized Without Further Worsening of Parkinsonism. This Report Focusses on The Synergistic Effects of Risperidone and Valproic Acid Inducing Parkinsonism.

INTRODUCTION

Drug-induced parkinsonism (DIP) is a well-established complication of certain medications, particularly antipsychotics. Parkinsonism is characterized by motor symptoms resembling those seen in Parkinson's disease, including tremors, bradykinesia, rigidity, and postural instability. Risperidone, a commonly prescribed atypical antipsychotic, works by blocking dopamine D2 receptors in the brain, which is effective in controlling symptoms of psychosis and mania. However, its dopamine-blocking properties can also impair the dopaminergic system, leading to EPS, particularly at higher doses. These motor side effects are a significant concern, particularly in long-term treatment. Risperidone is metabolized primarily by the cytochrome P450 (CYP2D6) enzyme in the liver. It has an active metabolite, 9-hydroxyrisperidone, which contributes to its overall therapeutic effects. The half-life of risperidone and 9-hydroxyrisperidone is relatively long (around 20 hours for risperidone and 24 hours for 9-hydroxyrisperidone), allowing for once-daily dosing. On the other hand, valproic acid, a mood stabilizer and anticonvulsant, is widely used in the management of mood disorders like bipolar disorder and epilepsy. Although primarily effective in reducing manic episodes and preventing seizures, valproic acid is not without side effects. Valproic acid is primarily metabolized in the liver by glucuronidation and oxidation (mainly via CYP2C9), and its metabolites are excreted in the urine. Hepatic dysfunction can significantly alter the drug's metabolism, leading to higher plasma concentrations.

When risperidone and valproic acid are prescribed together, the potential for drug-drug interactions that increase the risk of parkinsonism may arise. This phenomenon of drug-drug synergism occurs when the combination of these two medications results in enhanced dopaminergic dysfunction, leading to the emergence or exacerbation of motor symptoms. The interaction between risperidone's dopamine receptor antagonism and valproic acid's potential effects on the central nervous system may contribute to the development of drug-induced parkinsonism. This case report aims to explore the occurrence of drug-induced parkinsonism in a patient treated with both risperidone and valproic acid, highlighting the potential for synergistic effects that exacerbate parkinsonism. Understanding the underlying mechanisms of this interaction can assist healthcare providers in managing and mitigating the risks associated with combined use of these drugs.

Clinical Presentation:

A 59-year-old female with a medical history of schizophrenia and bipolar disorder, was being treated with risperidone (4 mg/day) for psychosis and valproic acid (290 mg/day) for mood stabilization for 16 years. The patient was now presented with complaints of resting tremor, bradykinesia, rigidity, postural instability and hypomimia. MRI screening of the brain suggested neurogenerative changes in the brain. Laboratory findings showed an elevation in the serum ammonia levels (102 µ mol/L). On admission the patient presented symptoms of parkinsonism, and risperidone was stopped abruptly, on further increase in the ammonia level, valproic acid was stopped gradually, leading to eventual decrease in serum ammonia level (93 µ mol/L) overtime.

Risperidone is acts on the D2 receptors present in the mesolimbic and nigrostriatal pathways. The nigrostriatal pathway is a key dopaminergic system involved in controlling movement. It

connects the substantia nigra (where dopamine is produced) to the striatum (important for motor coordination). Risperidone binds strongly to these receptors, which can lead to over-blockade of dopamine transmission. This strong receptor binding is a key factor in the development of parkinsonism because of the profound suppression of dopaminergic signalling in the nigrostriatal pathway. Valproic acid, an antiepileptic drug affects mitochondrial function, which is crucial for cellular energy production. The basal ganglia, particularly the substantia nigra, are highly dependent on proper mitochondrial function. It also enhances gamma-aminobutyric acid (GABA) activity, which is the primary inhibitory neurotransmitter in the brain. Overactivation of the GABAergic system could alter the balance of excitatory and inhibitory signals in the basal ganglia, contributing to the development of motor symptoms such as bradykinesia and rigidity. Hyperammonaemia is a major adverse effect caused by Valproic acid. Although the mechanism by which the pathway occurs is not fully understood, it is thought to interfere the urea cycle, particularly by inhibiting the activity of carbamoyl phosphate synthetase 1 (CPS1), the first enzyme in the urea cycle. CPS1 is essential for converting ammonia into urea. This results in the elevation of serum ammonia level. Ammonia is lipophilic in nature that can easily pass through the lipid layer covering the brain (Blood Brain Barrier). This can further damage the neurons through the destructive nature of ammonia. The patient conditions were managed by the gradual cessation of Risperidone and Valproic acid. To improve the extrapyramidal symptoms, T. AMANTIDINE (100mg P/O 1-0-1) and T. TRIHEXYPHENIDYL HYDROCHLORIDE (2mg P/O 1-0-0) were initiated along with physical therapy, speech therapy and other supportive measures. The patient had a gradual improvement when observed for the next few days.

DISCUSSION:

Although many studies have emerged showing the evidences of Risperidone induced parkinsonism as well as Valproic acid induced Parkinsonism, there are limited data showing the combined effect of both the drugs inducing Parkinsonism. Risperidone, a D2 receptor antagonist along with Valproic acid which is known to cause hyperammonaemia, slows down the extrapyramidal activities and damages the conducting cells of the brain (neurons) respectively leading to Parkinsonism. Even though these drugs are required for the effective management of other psychiatric conditions, it is important to frequently monitor the patients for extrapyramidal side effects and taper the doses if needed.

CONCLUSION:

The combination of risperidone and valproic acid can lead to a synergistic effect that exacerbates the risk of developing parkinsonism, a potentially debilitating condition. Clinicians should be aware of this interaction, especially in patients receiving both medications for the treatment of psychiatric and neurological disorders. Early recognition, prompt discontinuation or adjustment of the offending drugs, and appropriate symptomatic management are crucial to preventing long-term disability and improving patient outcomes.

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