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Case Report

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Intravenous Haldol Induced Seizures in an Agitated Patient on Scheduled Low Dose Risperidone



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ABSTRACT

Haloperidol [Haldol], a conventional antipsychotic of the butyrophenone class, blocks dopamine 2 receptors [D2] and causes side effects by D2 and alpha-1 blocking effects. Seizures are rarely reported in patients on Haloperidol and with poorly understood mechanisms. Risperidone [Risperdal] is a second-generation antipsychotic with antagonistic effects on serotonin 5-HT_{2A}, 5HT₇ and D2 receptors. Side effects occur by its action on alpha-1 adrenergic receptor and dopaminergic antagonism in different brain regions. Antipsychotics were reported to precipitate seizures. They also appear to pose a higher risk compared to first-generation antipsychotics, however, reports in the literature are rare and vary. We present a patient on medications that inhibit the isoenzymes involved in the metabolism of Haldol and Risperdal, leading to additive effects on lowering the seizure threshold causing new onset grand mal seizure. Associated risk factors include personal and family history of seizure, head injury, comorbid medical illness and genetic susceptibility which may be involved in this case.

INTRODUCTION

Haloperidol [Haldol], a conventional antipsychotic of the butyrophenone class, blocks dopamine 2 receptors [D2] and causes side effects by D2 and alpha-1 blocking effects. Seizures are rarely reported in patients on Haloperidol with poorly understood mechanisms. Among the typical antipsychotics, chlorprothixene and chlorpromazine have the highest risk [1,10]. Risperidone [Risperdal] is a second-generation antipsychotic with antagonistic effects on serotonin 5-HT_{2A}, 5HT₇ and D2 receptors. Side effects occur by its action on alpha-1 adrenergic receptor and dopaminergic antagonism in different brain regions [1]. Antipsychotics were reported to precipitate seizures. They also appear to pose a higher risk compared to first-generation antipsychotics, however reports in the literature are rare and vary [4,12]. We present a patient on medications that inhibit the isoenzymes involved in the metabolism of Haldol and Risperdal, leading to additive effects on lowering the seizure threshold causing new onset grand mal seizure.

CASE REPORT: K.T.M, a 75-year-old Caucasian male nursing home resident, was admitted for progressive fatigue, dizziness and exertional dyspnea. Additional symptoms included fever, chest pain and multiple episodes of near-syncope. His past medical history included diabetes, hypertension, chronic kidney disease, atrial fibrillation, coronary artery disease, dementia, depression, and chronic orthostatic hypotension. Urinalysis showed pyuria, thus treatment was started for possible urinary tract infection. Patient also treated for pneumonia due to a positive chest X-ray. Continued home medications included clopidogrel, Lopressor, fluconazole, Xarelto, fludrocortisone and fluoxetine at 40 mg daily. Psychiatry service was sought as patient became agitated and aggressive on the unit. Risperidone for delirium was gradually increased to 1 mg twice daily. On day two he became increasingly agitated thus Haldol 2 mg every 6 hours PRN was ordered. However, patient developed a primary generalized tonic-clonic seizure lasting for 2-5 minutes after the initial IV dose of Haldol with associated urinary incontinence, post-ictal confusion and weakness. Electroencephalogram post seizure was unremarkable as was the CT Scan, CBC, CMP, TSH, and EKG. Prolactin wasn't done but magnesium level was low at 1.7 mmol/dL [1.8-2.2 mmol/dL]. Initial laboratory results at admission were also unremarkable, except a creatinine level of 2.2 mg/dL [0.6-1.2 mg/dL] and HbA1C of 6.9% [<5.7%]. Haldol was discontinued immediately and patient never experienced another seizure. Team did not re-challenge patient with Haldol.

Enzymes involved in the pharmacokinetics of Haloperidol include cytochrome P450 (CYP), carbonyl reductase and uridine diphosphoglucose glucuronosyltransferase with observed variations in the catalytic activity of the CYP mediated reaction, but minimal variations in the glucuronidation and carbonyl reduction reactions. Haloperidol is a substrate of CYP3A4 and an inhibitor, and concurrently a stimulator, of CYP2D6. Risperidone is extensively metabolized by CYP2D6 and less by CYP3A4. Fluoxetine, conversely, has inhibitory effect on isoenzymes CYP2D6 and 3A4, besides 7% of Caucasians have a genetically inherited impaired activity of the CYP2D6 enzyme. Fluconazole is an inhibitor of the isozyme CYP2C19 (CYP3A4 and CYP2C9 to lesser extent) [6,7]. Hence, the steady state pharmacokinetics of Haldol and Risperdal is expected to change [increased levels of both] when co-administered orally with Fluconazole and Fluoxetine, which might explain the precipitation of seizure observed in our patient [6]. This patient got IV Haldol which bypasses the first-pass effect, leading to higher plasma levels than predicted. Risperdal may also have additive parasympatholytic effects paralytic ileus, hyperthermia, mydriasis, blurred vision, tachycardia, urinary retention, psychosis, and seizures [4,5] when used concomitantly with haloperidol. Despite receiving a benzodiazepine with anticonvulsant properties, he still had a seizure. The exact mechanism is unclear but related to the kindling effect of midbrain dopamine neurons excitation especially when administered over time. This might be applicable to Risperdal as in this case [9]. Different dopamine receptors were shown to mediate opposing influences on neuronal excitability and seizure precipitation, as the blockade of D2 is linked with seizure precipitation while blockade of D1 protects against seizures. [10]. Cases of seizures were reported in second-generation antipsychotics in a dose dependent fashion at about 0.1% for aripiprazole, 0.3% for Risperdal and 1-5% for clozapine [3,13]. New onset seizures have been reported in patients on Quetiapine and Risperdal, with seizurogenic conditions. Risperidone has an intermediate relative risk of causing seizures [2,8]. Associated risk factors include personal and family history of seizure, head injury, comorbid medical illness and genetic susceptibility which may be involved in this case. It is difficult to exclude the contribution of arrhythmias and hypotension in this patient. Though haloperidol and risperidone have low risk of inducing seizures compared to other antipsychotics, a combination of factors may have increased this patient's risk of seizures.

Caution is advised when prescribing these drugs to patients with risk factors for lowered seizure threshold including drug-drug interactions with medications that have potential pharmacokinetic or pharmacodynamic interactions.

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