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Case Report

Bradycardia and Hypotension Due to Co-Administration of Intramuscular Olanzapine and Lorazepam in a Schizophrenic Patient

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Abstract

Schizophrenia is a prevalent psychiatric disease classically considered one of the top 15 leading causes of disabilities worldwide. The prevalence of this disease, societal burden, and economic burden is not to be taken lightly. In the emergency room and psychiatric setting, schizophrenic patients often are admitted secondary to agitation. Frequently, medications are the treatment of choice for severe agitation refractory to verbal de-escalation. Great care must be considered in medication choice for agitation. We present a case of a 60-year-old male who suffered from hypotension and bradycardia after the administration of intramuscular olanzapine and lorazepam, together for severe agitation. The hemodynamic instability seems to be due to augmentation of both drugs mechanisms secondary to co-administration. Olanzapine is a Second Generation Antipsychotic (SGA) notable for more sedative properties and its alpha-1 antagonism may be the cause of hypotension. Additionally, the lorazepam mechanism of GABA potentiation only further summates patient sedation and hemodynamic instability. Complementing mechanisms and potent route of administration are a combination that can potentially become lethal. Updated prescription manufacturer information for olanzapine warns of possible cardiovascular compromise; furthermore, several of the cases used to ensure this warning had co-administration of benzodiazepines.

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Introduction

Worldwide prevalence of schizophrenia is about 1% [1] and it is amongst the top 15 leading causes of disabilities worldwide [2]. Suicide rate as per study by Palmer BA, 2005 is 4.9% [3] and per another study by Miles CP, 1977, it is 10% [4]. Schizophrenia puts enormous economic, and social burden on the patients, their families, caregivers, and the society. In US, the societal economic burden from schizophrenia has increased from $62.7 billion in 2002 to $155.7 billion in 2013, the major chunk (76%) of which is attributed to the indirect costs [5]. Agitation is a common sight in psychiatry units, emergency departments and long-term care facilities, and it's commonly seen in patients with schizophrenia spectrum disorders, bipolar disorders and substance use disorders. After verbal de-escalation has failed, the next step is to use medications for managing agitation. Widely used treatment for such patients, includes using antipsychotics and benzodiazepines. When choosing among the antipsychotics, SGAs have been recommended as the first choice of drugs by the American Association of Emergency Psychiatry [6], as they cause less Extrapyramidal Symptoms (EPS), and are as effective as First Generation Antipsychotics (FGAs) at controlling agitation [7]. For patients with agitation in a psychiatric disorder, such as bipolar disorder or schizophrenia, antipsychotics are preferred over benzodiazepines because they address the underlying psychosis. If, however, an initial dose of an antipsychotic does not control the agitation, the addition of a benzodiazepine is recommended over an increased dose of the same antipsychotic or addition of a second antipsychotic. Adding abenzodiazepine or anticholinergic agent to the antipsychotics increases the sedation and helps in decreasing the extrapyramidal symptoms. However, addition of benzodiazepines to antipsychotics have not consistently shown improved control of agitation and increases the risk of side effects, including over sedation and respiratory depression. In 2005, a warning was placed on olanzapine's prescribing information by Eli Lilly, after 160 post-marketing adverse events including 29 fatalities, in intramuscular olanzapine and 83% of these adverse events were associated with the concomitant use of benzodiazepines [8,9]. Currently, intramuscular olanzapine is the only SGA with a warning listed in FDA prescribing information. However, there were some limitations to these studies, as a few of the patients (n=14) had serious comorbid medical illness, 1 patient died of attempted suicide, and these reports did not specify about the formulation of benzodiazepine used. We present a case of a 60-year-old male who suffered from hypotension and bradycardia after the administration of intramuscular olanzapine and lorazepam, together for severe agitation.

Case Report

The patient is a 60-year-old Caucasian male with a past psychiatric history of unspecified psychosis and unspecified personality disorder, with extensive history of past inpatient psychiatric admission. The patient was brought to an emergency department by the EMS for altered mental status and worsening psychosis. He didn't have any other significant medical issues, his urine drug screen and blood alcohol were unremarkable. In the emergency department, patient was given olanzapine 10 mg and lorazepam 2mg intramuscularly before transfer to the inpatient behavioral health unit. After coming to the behavioral health unit, he became bradycardic and hypotensive, and his BP was noted to be in ranges 70-100's/40-60's, and his pulse dropped to 40s. He was sent back to the emergency department, where his heart rate was in the 40s and BP was ~80's/40's, EKG showed sinus bradycardia. Patients received 2L Normal Saline bolus after which his blood pressure improved to about 100/60. Poison control was contacted by the ED team and they stated that Olanzapine and Lorazepam combination is likely the cause of his presentation. Cardiology was contacted also after his Troponin came back elevated at 0.04 and they recommended trending troponins and EKG's and recommended against starting heparin unless his troponin continues to trend up. Subsequently, Troponins trended down to 0.01. His BP and HR continued to wax and wane for about 15+ hours. Echocardiography was also done due to his persistent low pressures after intravenous fluids, which showed a normal ventricular ejection fraction of 55-60%. Throughout his stay, he was overtly psychotic. After being medically stabilized, he was transferred back to behavioral health.

We reviewed literature and found 1 clinical trial evaluating the co administration of IV olanzapine and benzodiazepines, 1 retrospective study and a couple of case reports studying the adverse effects from giving olanzapine and benzodiazepines intramuscularly collectively [10,11]. To the best of our knowledge, we found one case report mentioning hypotension from co-administration of intramuscular olanzapine and lorazepam.

Discussion

Olanzapine is a second generation antipsychotic. It has a half-life of 31 hours and is in once-daily dosing. About 85% of olanzapine is absorbed from the GI tract, and about 40% of the dose is inactivated by first-pass hepatic metabolism. Olanzapine is an inhibitor of 5-HT2, Dopamine-1, 2, & 4, alpha-1 & 2, 5-HT1A, M1 to M5, and H1 receptors. It is highly sedating when compared to other SGAs. Furthermore, the alpha-1 receptor antagonism is the likely cause of persistent low blood pressure in the above described case. With intramuscular administrations, olanzapine's maximum concentration is 5 times higher than what is attained after oral administration. It has a chemical structure of thienobenzodiazepine, closely resembling to that of lorazepam. Benzodiazepines activate all three specific GABA–BZ binding sites of the GABAA-receptor, which opens chloride channels and reduces the rate of neuronal and muscle firing. When IM benzodiazepines and olanzapine are administered together, there is a higher chance of cardiorespiratory depression and sedation, given the similarities in their chemical structures [12]. Therefore, United States Food and Drug Administration warns against the co-administration of these two agents, but it does not outline a specific recommendation. The European Medical Agencies suggest that IM olanzapine and IM benzodiazepines should be at least 60 minutes apart. Clinicians should be thorough when prescribing this combination and administration should be followed with careful evaluation of side effects, which in some case reports have proven to be lethal. Until further research is conducted, clinicians must rely on available data and post marketing surveillance as a reflection of drug safety.

Conclusion

In managing the acute psychosis of a schizophrenic patient, earlier point of care sites must take caution in the co-administration of olanzapine and lorazepam. Evidence suggests the augmentation of both drug mechanisms through co-administration, may precipitate life threatening hemodynamic instability.

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