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Drug-Induced Delirium from a Suspected Drug-Drug Interaction between Promethazine and Ketorolac

Case Report

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Abstract

Case: An 18 year old female with no psychiatric history experiences delirium following the administration of promethazine and ketorolac which resolves following the discontinuation of both medications. The pathophysiology of drug-induced delirium has not been well established and is thought to be multifactorial. Delirium has been independently associated with both promethazine and ketorolac through different mechanisms. The objective of this case report is to describe a suspected synergistic drug-drug interaction between promethazine and ketorolac presenting as drug-induced delirium.

Conclusion: There appears to be a synergistic drug-drug interaction between promethazine and ketorolac presenting as acute drug-induced delirium. Clinicians should consider withdrawing both medications should psychiatric adverse effects appear or are exacerbated when promethazine and ketorolac are used concomitantly.

Keywords: Promethazine; Ketorolac; NSAIDs; Delirium; Drug-Drug Interaction.

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Introduction

Drug-induced delirium is an adverse effect associated with a multitude of medications. It is most commonly occurs in elderly patients with as many as one in five hospitalized geriatrics experience delirium subsequent to medications [1-4]. However, it is important to note that drug-induced delirium can occur at any age. Though reversible upon discontinuation of the offending agent(s), the occurrence of delirium is known to increase hospital stays and mortality risk.

The pathophysiology of drug-induced delirium has not been well established and is suspected to be multifactorial. The dopaminergic, cholinergic, GABAergic, serotonergic, and glutamatergic modulatory systems have all been proposed as possible pathways, but the exact pathophysiology remains uncertain [1-3]. Most drugs known to induce or exacerbate delirium are thought to do so through one of these pathways [2].

Promethazine exerts its effects by antagonizing to varying degrees histamine 1, dopamine, alpha1 adrenergic, and muscarinic acetylcholine receptors [5-6]. Although it has multiple indications, promethazine is primarily used to manage nausea and vomiting. The antiemetic properties of promethazine can be attributed in part to the blockade of central dopamine and histamine receptors but is primarily associated with its anticholinergic properties. Any anticholinergic medication in sufficient doses can potentiate a deleterious effect, but agents with affinity for the muscarinic receptors, as seen with promethazine, exert the strongest association between medication use and delirium[3,5]. New memory acquisition and stored memory retrieval is impaired, an action which is attributed to the cholinergic system's influence on information processing [4].

Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to induce delirium as well[1,3-4]. The incidence appears to be the highest with indomethacin, but all NSAIDs can induce or exacerbate psychiatric symptoms, including delirium [3-4,7-8]. The pathophysiology of NSAID induced psychiatric effects is not clearly established. It has been suggested that the chemical structure of NSAIDs, particularly the indolic moiety of indomethacin, is similar to that of serotonin and therefore delirium occurs at least in part via the serotonergic pathway [3, 9]. The psychiatric effects abate when the offending agent is withdrawn and reappear when reintroduced, providing strong support that the effects are drug-induced [7-8]. Details of ketorolac-specific induced behaviour change are scarce though the product labelling includes psychiatric symptoms as potential adverse effects.

Despite both agents being able to potentiate delirium, no known interaction between promethazine and ketorolac has previously been thought to exist. The objective of this case report is to describe a suspected synergistic drug-drug interaction between promethazine and ketorolac presenting as drug-induced delirium.

Case Description

An 18 year old Caucasian female presented to the emergency room (ER) during the morning with a one day history of nausea, vomiting, chills, and vague abdominal pain. She reported her vomit as greenish in color and non-bloody. There was no evidence of fever, recent travel, contact with sick persons, or diet changes. She had been hospitalized approxi-

mately six weeks prior for acute gastroenteritis but was otherwise healthy. The only medication she took as an outpatient was minocycline of acne. The patient denied using illicit drugs, but admitted alcohol intake as recently as two nights prior to admission.

The patient's physical exam in the ER was normal except for some abdominal tenderness and right sided guarding. A complete metabolic panel (CMP) and complete blood count (CBC) were ordered on admission to the ER. The laboratory values were within normal limits with the exception of hypokalemia (3.1 mEq/L), hyperglycemia (164 mg/dL) and an elevated white blood cell (WBC) count (12,400 cells/mL). Both the pregnancy test and urine drug screen conducted were negative. A urinalysis was also performed and did not indicate any abnormalities or infection. While in the ER, she received an injection of promethazine 25 mg. Approximately one hour after the promethazine administration she was noted to be thrashing and moving around in her bed. The movements subsided and on the next assessment two hours later, the patient was observed to be resting quietly.

The patient was admitted to the hospital that evening for further evaluation and orders for intravenous fluid replacement (Dextrose 5% and normal saline with 20 mEq potassium chloride) and promethazine 25 mg intravenously as needed for nausea and vomiting were written. Through the course of the first night, the patient continued experiencing emesis despite two additional promethazine 25 mg injections. She was noted to be considerably anxious and periodically would thrash around erratically in the bed. The patient was given a one-time intravenous dose of lorazepam 1mg which was successful in sedating the patient who rested comfortably for the remainder of the night.

After awakening the following morning, the patient once again experienced continuous vomiting. She was given ondansetron which appeared to elevate her symptoms. The patient continued to complain of abdominal pain and display left sided guarding. Though not febrile at admission, a temperature of 100.8º F (38.2°C) prompted a urinalysis, blood and urine cultures, and a computerized topography (CT) of the abdomen, none of which indicated infection or other abnormalities. A CMP was also conducted that morning and all laboratory values were normal with the exception of resolving hypokalemia (3.3 mEq/mL) for which she received potassium chloride 40 mEq by mouth.

The patient received two additional doses of promethazine for her continued nausea and vomiting. Her anxious and erratic behavior and abdominal pain also continued throughout the day. Her nausea and vomiting was eventually controlled with the addition of scheduled intravenous ondansetron 4 mg. Due to ongoing abdominal pain and nausea the evening of the second night of her hospital stay, the patient received an intravenous dose of ketorolac 60 mg with her promethazine 25 mg injection. After the administration of both agents, the patient's behavior became even more increasingly erratic. She began thrashing around in her bed with more force than previously seen and attempted to disrobe and expose herself to the nursing and medical staff present. The patient did not respond to nor elicit any verbal communication. This behavior continued until the early morning when the patient eventually fell asleep.

The following morning, the patient stated that she had no recollection of this behaviour and appeared calm. The order for as need promethazine was discontinued, but the patient continued to receive the ondansetron which was successful in controlling her nausea and vomiting. After consultations from surgery and gastroenterology, the patient was diagnosed with mild gastritis and duodenitis.

Because the patient did not have any known psychiatric history, her behaviour was suspected to be a result of promethazine, ketorolac, or a combination of both medications. We did not suspect ondansetron or any drug-interaction involving ondansetron because the erratic behavior appeared before the administration of ondansetron, did not increase when ondansetron alone was added to promethazine, but did increase markedly when ketorolac was added to the promethazine regimen. Both promethazine and ketorolac were discontinued and no additional doses were administered. The patient did continue to receive the scheduled ondansetron which alleviated her symptoms. She did not exhibit any additional abnormal behavior throughout the remainder of her hospitalization and was discharged on day four of her hospital stay.

Discussion

We present a case of drug-induced delirium that presented following promethazine and ketorolac administration. Though the patient experienced delirium-like symptoms following administration of promethazine alone, her erratic behavior peaked following administration of ketorolac. The patient did not have a history of psychiatric illness other potential risk factors for delirium, such as infection, were not considered to be contributory to this patient's altered behavior. Although the patient's initial WBC was slightly elevated, she was correspondingly afebrile and had no other signs of infection. The mildly elevated temperature on the second day of admission was incidental with no additional supporting features of infection. Furthermore, all symptoms resolved following the removal of the offending agents thus supporting the suspicion that her delirium was drug-induced. It is possible that pain may have contributed to the patient's delirium, but given the close proximity and consistency in delirium presentation following the administration of promethazine and ketorolac; it was not thought to be a significant etiology. Our patient did receive a one-time dose of lorazepam, also associated with delirium [3]. However, no delirious effects occurred following lorazepam, and the drug's short duration and half-life make it an unlikely etiology for this patient's symptoms.

To our knowledge, this is the first report of a drug-drug interaction between promethazine and ketorolac and the first clinical report of delirium following ketorolac use. Because single pathophysiologic mechanisms of drug-induced delirium are not well understood, the influence of concurrent action of multiple pathways or multiple medications acting upon the same pathway cannot be well elicited. Since promethazine and ketorolac are thought to induce psychiatric effects via different pathways, it would be reasonable to consider that the interaction is synergistic. Several published cases of delirium occurred following supertherapuetic doses of promethazine, but delirious effects have been reported following therapeutic doses, as with our patient [5-6].

This report also involves drug-induced delirium associated with ketorolac, which has been reported in product labeling, but not detailed in readily available primary literature. All NSAIDs are thought to be able to induce or exacerbate delirium, though most cases have been associated with indomethacin [9]. Ketorolac is a pyrrole acetic acid derivative and structurally related to indomethacin [10]. Although a small lipophilic molecule, it is highly protein bound in plasma and does not distribute across the blood brain barrier (BBB) as readily as other agents within the class. Indomethacin's penetration across the BBB is also thought to be less than other NSAIDs, but evidence indicates that efflux-proteins at the BBB help facilitate the transfer of indomethacin into the central nervous system (CNS) [10]. The role of transporters with ketorolac remains unknown, but given the structural similarities between ketorolac and indomethacin, entrance into the CNS by transporters may explain the psychiatric adverse effects of ketorolac (15). Altered kidney function, which may associated with NSAID use, is also a risk factor for delirium. Our patient did not have any indications of altered or changing kidney function throughout her hospital stay.

The emergence of delirium in our patient following promethazine and ketorolac administration that subsided after the withdrawal of both agents suggests a drug-drug interaction between two medications associated with psychiatric adverse effects not previously thought to interact. The only beforehand known drug-drug interaction producing psychiatric effects involving NSAIDs is an increased risk of lithium toxicity secondary to a decreased renal clearance by NSAIDs. Our patient did not have a history of lithium use nor received it while hospitalized.

Conclusion

Promethazine and ketorolac are used together commonly in acute illness and it is possible that such an interaction occurs but is underreported.

Although not present in our patient, other risk factors for delirium, including infection, pain, or altered kidney function may make it difficult to clearly associate delirium with the use of these medications. Also, because the psychiatric effects of promethazine are better understood, delirium presenting when these agents are used concurrently may be erroneously attributed to promethazine alone. Clinicians should be aware of this potential effect and consider withdrawal of both promethazine and ketorolac should psychiatric symptoms appear or are exacerbated in a patient receiving both agents concomitantly.

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Conflicts of Interest Statement

None of the authors of this manuscript have any conflicts of interests to disclose.

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