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Panic Attack Following Addition of Nalmefene to Methylphenidate in a Patient with Comorbid Alcohol Use Disorder and Attention Deficit Hyperactivity Disorder: A Case Report

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Case Study

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ABSTRACT

Aim: Our aim is to describe a previously unreported potential interaction of nalmefene with methylphenidate and discuss possible mechanisms and precautions.

Presentation of Case: A 40-year-old man with ADHD taking long-acting methylphenidate developed alcohol use disorder. Nalmefene was prescribed. Following his first bedtime administration, he awoke with panic attack symptoms and concomitant suicidal and homicidal ideation. These symptoms resolved 45 minutes after he received diazepam.

Discussion: Hypotheses for this reaction include a previously undescribed nalmefene–methylphenidate interaction causing elevated levels of either drug and leading to anxiety and panic symptoms, dysphoria, and suicidal/homicidal ideation. ADHD and alcohol abuse disorder are common comorbidities and treatment with both methylphenidate and nalmefene is a reasonable approach.

Conclusions: The patient described in this case had not previously reported any of these adverse events, reported them on the first and only occasion of ingesting methylphenidate and nalmefene on

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the same day, and has not reported them since, suggesting that the adverse events may have been associated with a drug–drug interaction. However, our experience with this case suggests that further research is required on this potential interaction and that clinicians should be aware of this potential interaction and use caution in prescribing this combination.

Keywords: Nalmefene; homicidal thought; methylphenidate interaction; panic attack; psychiatric adverse effect; suicidal thought.

1. INTRODUCTION

Alcohol use disorder is a frequent co-morbidity in adult attention deficit hyperactivity disorder. Nalme fene is a unique opioid receptor modulator used in the management of alcohol dependence. In vitro studies have shown that nalmefene is a selective opioid receptor ligand that is an antagonist at both μ and δ opioid receptors and a partial agonist at κ opioid receptors. In vivo studies have shown that nalmefene decreases alcohol consumption and that this is effect is likely through modulating corticomesolimbic functions [1].

Methylphenidate is a psychostimulant drug. It inhibits both the dopamine transporter, particularly in presynaptic neurons of the nucleus accumbens, and the norepinephrine transporter, particularly in the prefrontal cortex. This inhibition by methylphenidate of the dopamine and norepinephrine transporters effectively blocks the reuptake of these neurotransmitters into the cell and results in their increase in the extra-neuronal space [2].

Thus, nalmefene and methylphenidate act on different neurotransmitter systems and have not previously been reported to interact. Simultaneous prescription of these medications is not currently contraindicated and would thus appear appropriate where warranted. However, we present a case here in which we describe a possible interaction of nalmefene with methylphenidate. We also discuss mechanisms that might explain such an occurrence. Because this potential drug–drug interaction has not been previously described, it is reported here to alert clinicians to the possibility and to suggest appropriate precaution in prescribing this combination.

2. PRESENTATION OF CASE

A 40-year-old, married, father of two children who was a practicing physician attended a psychiatric outpatient clinic as a patient. The reason he gave for his attendance was to decrease or stop his alcohol consumption because his alcohol use was causing problems between him and his wife. For nearly 5 years, he had been drinking three to four bottles of beer each day, 5–6 days per week. When his alcohol consumption began, he drank a lower amount and less frequently, but this gradually increased. Over the preceding 7 years, he had experienced 1–2 months per year that were alcohol-free (e.g., every year during important religious times). During those times of abstinence, he abruptly stopped consuming alcohol and experienced no serious effects, except for a few days of mild insomnia. The patient had no history of delirium tremens or withdrawal symptoms during his abstinence from alcohol and no history of anxiety disorder, panic disorder, or panic attack, as well as no history of suicidal or homicidal ideation or any affective disorder. A full psychiatric history was taken to exclude other comorbid psychiatric conditions. The patient's functionality was good and he did not have any problems concerning his job.

As a child, the patient was vibrant, energetic, cheerful, hyperthymic, and impatient. He also experienced problems with focusing and easily became bored when engaged in cognitive activities, such as reading a book or attending to academic lessons. However, he was not taken to a psychiatrist as a child. Two years preceding his visit to the psychiatric outpatient clinic, he was diagnosed as having "severe" ADHD and began taking long-acting methylphenidate (54 mg/day) for this disorder. The diagnosis was made by a psychiatrist based on the criteria describe in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5).

A psychiatric examination was conducted on the day he arrived at the psychiatric outpatient clinic. His appearance, manner, and behavior were normal, and he was cooperative. His speech was spontaneous and normal, with the amount spoken within normal limits, suggesting that his impulse control was also normal. He was fully awake and alert throughout the interview, with his orientation to people, place, and time intact.

His thoughts were logically associated and goal directed, with no delusion or obsession apparent. His abstract thinking appeared to be normal. He reported no perception abnormalities. Both his recent and long-term memory were intact. He appeared mildly anxious, and his psychomotor activity was mildly increased.

The patient was diagnosed as having alcohol use disorder by a psychiatrist based on DSM-5 criteria, and it was recommended that he attend an alcohol dependency inpatient clinic. However, he was reluctant to be hospitalized. In the first visit, he was prescribed nalmefene at a dose of 18 mg/day and cautioned not to quit drinking but instead to decrease the amount of alcohol consumed.

On the day the patient first ingested nalmefene, he consumed no alcohol and did not have any problems during the day. At 6:00 p.m., he took his regular prescribed dose of long-acting methylphenidate (54 mg). At 8:45 pm., he ingested 18 mg of nalmefene. At 9:30 p.m., he went to sleep. At 10:30 p.m., he awoke with intense feelings of anxiety and choking, shortness of breath, discomfort in his chest, restlessness, and suicidal and homicidal thoughts (of killing his wife and child).

He presented to the emergency department of a state hospital. His laboratory test results assessed after he arrived in the emergency department indicated that his hepatic enzymes and values of the standard biochemicals depicting renal function were within reference ranges. Additionally, his vitamin B 12, folic acid, and thyrotropin levels as well as his complete blood count values were within reference ranges. Tests assessing cardiac function, including electrocardiograms recorded the day of the adverse reaction in the emergency department and the following day, were normal except for the presence of tachycardia. His pulse rate was 100 bpm and his respiratory rate was 24 breaths/min. The results of toxicological screens (amphetamine, methamphetamine, cocaine, tetrahydrocannabinol, and opiates) of his urine were negative. He was given diazepam (5 mg per os) by a psychiatrist. His panic peaked within a few minutes of consuming the diazepam and was resolved within 35–40 min. He returned home and went to sleep until the morning without any further problem. Nalmefene was discontinued and the symptoms did not recur.

At his 6- and 12-month follow-up appointments, the patient reported no incidences of panic attack or suicidal or homicidal thoughts. He continued taking methylphenidate (54 mg/day) and reported maintaining a decreased amount and frequency of alcohol consumption (2–3 beers/day, 2–3 days/week).

3. DISCUSSION

Prior to the adverse events reported here, the patient was taking methylphenidate without complications or concerns. The first time he ingested nalmefene on the same day as taking methylphenidate, he experienced the adverse events.

Dopamine (DA) is thought to be related to aggressive and antisocial behavior through its role in the initiation and execution of behavior and in behavioral reinforcement [3]. Aggressive behavior depends on intact DA neurons in the mesocorticolimbic pathways. The ascending dopaminergic projections from the ventral tegmental area to the ventral striatum, including the nucleus accumbens, and to the prefrontal cortex are critical for initiating certain types of aggressive behavior. Measurements of elevated DA activity in postmortem tissue of aggressive mice and rats have been used to establish an important link between aggression and DA in the frontal cortex, ventral striatum, and nucleus accumbens [4]. In the present case, nalmefene may have increased methylphenidate blood levels through an unknown mechanism. The increased methylphenidate levels may have led to increased dopaminergic neurotransmission and caused homicidal thoughts. The physician's insert for methylphenidate lists thinking about or feeling like killing oneself as uncommon adverse effects.

The increased methylphenidate blood levels may also have led to the panic attack, as anxiety is a well-known and common adverse effect of methylphenidate. Dopamine plays an important role in anxiety, modulating the cortical "brake" that the medial prefrontal cortex exerts on the anxiogenic output of the amygdala [5]. Although it is also possible that the panic attack experienced was due to life stressors, the patient did not report experiencing another panic attack at the 1 year follow-up, suggesting that this adverse event was more likely associated with a drug–drug interaction.

It is also plausible that methylphenidate increased the blood levels of nalmefene through an unknown mechanism and that these increased blood levels led to palpitation and restlessness—which are noted as common adverse effects in the physician's insert for nalmefene—as well as the other panic symptoms. Nalmefene may cause panic attack by affecting the mesocorticolimbic dopaminergic transmission through its kappa opioid receptor modulating effects, as selective kappa opioid receptor agonists produce negative mood states, including dysphoria and anxiety [6-9].

The patient's suicidal thoughts may also have been related to an unknown interaction between methylphenidate and nalmefene.

The adverse events experienced by the patient may have been also due to a specific reaction to the nalmefene itself. But at the 1 year follow-up although he took nalmefene only (on days he did not take methylphenidate) occasionaly, he did not experience any of the side effects mentioned above. So according to us, this rules outs the possibility of a specific reaction to the nalmefene itself.

Although the mechanisms remain obscure, the potential for an interaction between these two commonly prescribed medications required that we report this case to identify the possibility to other clinicians and to suggest appropriate precautions in combining methylphenidate and nalmefene.

The limitations associated with interpreting the results described in our case report include the following: the absence of testing to confirm excessive drug levels in the patient's blood, the possibility that psychosocial factors contributed to the occurrence of the panic attack, and the absence of any test–retest data that would confirm the ability to elicit these symptoms by exposure to the drug combination.

4. CONCLUSION

Nalmefene has not been sufficiently investigated in patients with unstable psychiatric disease, and no warning of a potential interaction with methylphenidate is included in the physician's insert for nalmefene. However, ADHD and alcohol abuse disorder are common comorbidities and treatment with both methylphenidate and nalmefene is a reasonable approach. The patient described in this case had not previously reported any of these adverse events, reported them on the first and only occasion of ingesting methylphenidate and nalmefene on the same day, and has not reported them since, suggesting that the adverse events may have been associated with a drug–drug interaction. This study found that, clinicians should be aware of this possible interaction and that caution may be necessary in prescribing this combination.

CONSENT

Author declares that 'written informed consent was obtained from the patient for publication of this case report.

ETHICAL APPROVAL

Author hereby declares that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Soyka M. Nalmefene for the treatment of alcohol dependence: A current update. Int J Neuropsychopharmacol. 2014;17(4): 675-84.
2. Volz TJ. Neuropharmacological mechanisms underlying the neuroprotective effects of methylphenidate. Curr Neuropharmacol. 2008;6(4):379-85.
3. Ishikawa S, Raine A. Behavioral genetics and crime. In Glicksohn J, editor. The Neurobiology of Criminal Behavior. 1st ed. Kluwer Academic Publishers; 2002.
4. Miczek KA, Fish EW. Monoamines, GABA, glutamate, and aggression. In Nelson RJ, editor. Biology of Aggression, 1st ed. Oxford University Press; 2006.
5. de la Mora MP, Gallegos-Cari A, Arizmendi-Garcıa Y, Marcellino D, Fuxe K. Role of dopamine receptor mechanisms in the amygdaloid modulation of fear and anxiety: Structural and functional analysis. Prog Neurobiol. 2010;90(2):198-216.
6. Carr GV, Lucki I. Comparison of the kappa-opioid receptor antagonist DIPPA in

tests of anxiety-like behavior between Wistar Kyoto and Sprague Dawley rats. Psychopharmacology (Berl). 2010;210(2): 295-302.

7. Wiley MD, Poveromo LB, Antapasis J, Herrera CM, Bolaños Guzmán CA. Kappa-opioid system regulates the long-lasting behavioral adaptations induced by early-life exposure to methylphenidate. Neuropsychopharmacology. 2009;34(5): 1339-50.

8. Van't Veer A, Carlezon WA Jr. Role of kappa-opioid receptors in stress and anxiety-related behavior. Psychopharmacology (Berl). 2013;229(3): 435-52.

9. Knoll AT, Meloni EG, Thomas JB, Carroll FI, Carlezon WA Jr. Anxiolytic-like effects of kappa-opioid receptor antagonists in models of unlearned and learned fear in rats. J Pharmacol Exp Ther. 2007;323(3): 838-45.

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