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Xanomeline/trospium-induced polyuria: A patient case report

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Abstract

Xanomeline/trospium is a newly approved agent for the management of schizophrenia. Unlike traditional antipsychotics, which are D_2 receptor antagonists, xanomeline is an M_1/M_4 muscarinic acetylcholine receptor agonist coformulated with trospium, a peripheral muscarinic antagonist. The addition of the trospium constituent aims to reduce or prevent the peripheral effects of muscarinic acetylcholine receptor agonism by xanomeline, which would include classic cholinergic adverse effects such as increased salivation, defecation, and urination. The package insert reports that some of the most frequently observed adverse reactions (incidence $\geq$5%) throughout clinical trials were those congruent with the expected anticholinergic effects of trospium, such as urinary retention and constipation, as well as other reactions that likely coincide with xanomeline use, such as nausea, vomiting, and diarrhea.[1] However, there is no documented incidence of polyuria secondary to xanomeline/trospium use in the current literature. We present a case of a 53-year-old White male who was treated with xanomeline/trospium for the management of schizophrenia who experienced polyuria after a dose titration to maximum dosing of xanomeline/trospium 125 mg/30 mg by mouth twice daily. Owing to the emergence of polyuria 3 days after the dose titration, the xanomeline/trospium was discontinued after discussion with the provider, and the polyuria resolved within 1 day.

Keywords: xanomeline/trospium, polyuria, muscarinic receptor agonist, cholinergic effects, schizophrenia

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Introduction

Xanomeline/trospium is a novel agent that was approved in September of 2024 for the treatment of schizophrenia in adults. Unlike traditional antipsychotic medications that are primarily dopamine receptor antagonists, xanomeline is an agonist at the M_1 and M_4 muscarinic acetylcholine receptors. The mechanism by which xanomeline elicits psychotropic effects is not entirely understood.[1] However, the activation of muscarinic acetylcholine receptors is theorized to be involved in a reduction of dopamine transmission within the mesolimbic pathway, specifically through dopamine efflux within the striatum,[2] lending utility in managing the positive symptoms of schizophrenia. Owing to the mechanism of action avoiding direct dopamine receptor blockade, xanomeline demonstrated in clinical trials to avoid many of the signature adverse effects observed with traditional dopamine antagonists, such as weight gain, hyperprolactinemia, and extrapyramidal symptoms.[1]

Xanomeline favorably crosses the blood-brain barrier, which allows it to induce its psychotropic effects within the brain. However, muscarinic receptor agonism within the periphery can result in various systemic effects, notably increased secretory mechanisms such as salivation, defecation, vomiting, and urination. To mitigate these effects, xanomeline is coformulated with trospium chloride, a peripheral muscarinic antagonist that does not cross the blood-brain barrier, to block these peripheral effects of

xanomeline while still allowing it to remain active within the brain. Here, we present the case of a 53-year-old male who experienced polyuria secondary to an increase in the dose of xanomeline/trospium.

Case Report

The patient was a 53-year-old White male who presented to the emergency department for increased depression, suicidal ideation, and command auditory hallucinations. The patient's past medical history was significant for chronic systolic heart failure, type 2 diabetes mellitus, schizoaffective disorder, and depression. The patient's previous pertinent home drug regimen consisted of clozapine 200 mg by mouth twice per day, divalproex extended-release 1250 mg by mouth at bedtime, glycopyrrolate 1 mg by mouth 3 times per day, sacubitril/valsartan 24 mg/26 mg by mouth twice per day, and empagliflozin 10 mg by mouth once per day. The patient was reported to be adherent to these medications before admission, as documented by the patient's community treatment program, and they were continued upon admission on hospital day 0 (HD 0). On HD 3, the patient requested to be off clozapine due to adverse effects, most notably sedation, and unwillingness to comply with bloodwork for neutrophil count monitoring. Therefore, clozapine was discontinued along with glycopyrrolate as this medication was being used for sialorrhea secondary to clozapine use, and aripiprazole was initiated at 10 mg by mouth once per day. The aripiprazole was titrated from 10 mg by mouth daily to 30 mg by mouth between HD 3 and HD 8. Owing to a lack of therapeutic response and the patient continually responding to internal stimuli, the aripiprazole 30 mg was discontinued, and xanomeline/trospium was initiated at 50 mg/20 mg by mouth twice per day, before breakfast and at bedtime, on HD 8. The treatment team decided to start xanomeline/trospium due to the avoidance of many adverse effects that are prevalent with traditional antipsychotics, especially sedation, as this was the patient's main reason for wanting to discontinue clozapine initially. The patient received 4 doses of xanomeline/trospium 50 mg/20 mg by mouth twice per day over 3 days, after which the dose was increased to 100 mg/20 mg by mouth twice per day on HD 10. The patient received xanomeline/trospium 100 mg/20 mg by mouth twice per day for 16 days without incident and demonstrated some improvement in symptoms during that time. The patient improved by becoming increasingly conversational and engaged in his treatment, but still would respond to auditory hallucinations. On HD 26, the patient was noted to be actively responding to internal stimuli and was no longer redirectable, which had not been the case over the previous 16 days. Owing to continued symptoms, the xanomeline/trospium dose was increased to the maximum dose of 125 mg/30 mg by mouth twice per day on HD 26. It was at this point that olanzapine 10 mg by mouth at bedtime was also added for increased stabilization. After 3 days of xanomeline/trospium 125 mg/30 mg by mouth twice per day and olanzapine 10 mg by mouth at bedtime, the patient began to develop polyuria and subsequent urinary incontinence throughout the day on HD 29, as noted in nursing and psychiatrist chart documentation. Documentation also reflected that the patient was urinating uncontrollably in large volumes throughout his room, including the patient's bedding and floor. Upon this development, the clinical pharmacist was consulted to review the patient's medications for potential adverse reactions, and they discussed with the provider to consider reducing the dose of xanomeline/trospium back to 100 mg/20 mg by mouth twice per day. After dose reduction of xanomeline/trospium, the polyuria subsided on HD 31 and did not return throughout the remainder of the patient's admission. Because of the lack of therapeutic benefit of xanomeline/trospium at 100 mg/20 mg by mouth twice per day, it was discontinued entirely on HD 32, and the olanzapine was maintained as his psychiatric regimen without any noted adverse effects. After discontinuing xanomeline/trospium, the olanzapine was further titrated to 15 mg by mouth at bedtime on HD 32, and this dose was maintained for an additional 5 days of therapy. Ultimately, the olanzapine was ineffective and was therefore discontinued on HD 37, and at this time, the treatment team met with the patient to discuss a care plan. The patient was agreeable to restarting clozapine. After initiating clozapine 25 mg by mouth twice daily on HD 37 and subsequent titration up to 100 mg by mouth twice daily by HD 40, the patient was no longer internally preoccupied or responding to auditory hallucinations, and he was ultimately discharged on clozapine 100 mg by mouth twice daily on HD 45.

Discussion

This case illustrates an incidence of polyuria secondary to xanomeline/trospium use, despite the most familiar side effects of the medication being anticholinergic due to the expected peripheral action of trospium. Although xanomeline is categorized as an M_1/M_4 muscarinic acetylcholine receptor agonist, there is some evidence that it may interact with other muscarinic acetylcholine receptor subtypes[3,4]; most notably, the M_3 muscarinic acetylcholine receptor, which is implicated in urinary function in humans.[5] Specifically, M_3 muscarinic acetylcholine receptor agonism results in detrusor muscle contraction leading to urination. Therefore, this patient case may be explained by the off-site agonism at the M_3 muscarinic acetylcholine receptor. The mechanism by which the xanomeline may have contributed to this case of polyuria can be understood if the trospium concentration was not sufficient to counteract the effects of xanomeline after-dose titration, and therefore resulted in peripheral muscarinic effects. Furthermore, the resolution of the polyuria after decreasing the xanomeline/trospium dose back to 100 mg/20 mg and then subsequently discontinuing the medication completely may further explain the presence and subsequent resolution of this unexpected adverse event.

Additionally, the Adverse Drug Reaction Probability Scale (Naranjo) was completed for this case, yielding a score of 6, indicating a probable interpretation.[6]

When reviewing other possible etiologies for this case, other potential contributory medications were ruled out as there were no changes made to the patient's home regimen outside of antipsychotic selection. Furthermore, the patient was tolerating all home medications before admission without any reports of urinary adverse events, despite adherence to empagliflozin and sacubitril/valsartan, which have known associated urinary adverse events. The patient's diabetes was also controlled throughout admission, as evidenced by documented blood glucose readings that were within normal limits, and the patient did not exhibit any urinary symptoms before the incidence of polyuria. The patient also did not have any degree of renal dysfunction throughout the hospital course.

Conclusion

This case of polyuria secondary to xanomeline/trospium use highlights the need for clinicians and patients alike to monitor for the possibility of polyuria and potentially other similar cholinergic adverse events to occur with the use of this medication in the management of schizophrenia, despite the aim of the addition of trospium being to prevent these effects in the periphery.

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