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Diltiazem for clozapine-induced generalized hyperhidrosis

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Abstract

Background: Clozapine can be associated with significant side effects and tolerability issues. Hyperhidrosis occurs less commonly and is unanticipated by clinicians because of clozapine's significant anticholinergic activity.

Case Report: A 34-year-old female developed clozapine-induced nocturnal, generalized hyperhidrosis following initial titration to 400 mg/day. Dose reduction did not decrease the side effect. Treatment with an anticholinergic medication could not be initiated because of constipation. Treatment with a beta blocker resulted in worsening of asthma. Treatment with a calcium channel blocker, diltiazem CD 180 mg/day, resulted in a significant reduction in hyperhidrosis.

Conclusion: This case supports the use of calcium channel blockers to reduce clozapine-induced hyperhidrosis and offers an alternative to anticholinergic medications that may negatively impact clozapine tolerability.

Keywords: hyperhidrosis, clozapine, calcium channel blocker, diltiazem

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Background

Clozapine is the only FDA-approved antipsychotic indicated for treatment-resistant schizophrenia. The drug also has approval for reduction in the risk of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder.[1] Clozapine is a life-changing medication that is underused in the United States; one reason being its association with significant side effects and tolerability issues.[2] *Sweating* was reported in 6% of research subjects participating in clozapine clinical trials.[1] Hyperhidrosis, excessive sweating, is not listed as a side effect in the package labeling and it is unclear if *sweating* or diaphoresis implied hyperhidrosis in the trials. Etiology of clozapine-induced hyperhidrosis is not well defined and may be overlooked by some clinicians as clozapine is associated with strong anticholinergic side effects.[1] Muscarinic receptors, specifically M_1 and M_3, are found in the exocrine glands, and clozapine's partial agonist activity at these receptors may be responsible for hyperhidrosis.[3,4] A literature search resulted in only 1 case report describing clozapine-induced hyperhidrosis.[5] Richardson et al described a case of clozapine-induced hyperhidrosis treated with biperiden, a muscarinic antagonist no longer available in the United States specific for the M_1 receptor. We report a case of clozapine-induced hyperhidrosis treated with the nondihydropyridine calcium channel blocker, diltiazem.

Case

A 34-year-old female was hospitalized because of psychosis associated with an 11-year history of schizophrenia characterized by systematized religious delusions involving

TABLE: Commonly used medications for generalized hyperhidrosis

Name	Dosing	Drug Interactions	Contraindications/Warnings	Common Side Effects
Benztropine	0.5 mg by mouth twice daily	Avoid combining with medications that have anticholinergic activity because of increased risk of adverse effects	Use with caution in glaucoma, obstructive GI disease, and uropathy	Dry mouth, blurred vision, tachycardia, constipation, urinary retention, and memory impairment
Clonidine[a]	0.1 mg by mouth twice daily	Avoid combination with CNS depressants Clonidine is a CYP450 1A2/2D6/3A4/5 substrate – hypotensive effect can be exacerbated with concomitant use of a CYP450 1A2/2D6/3A4/5 inhibitors	Sedation Withdrawal syndrome associated with abrupt discontinuation	Sedation, dry mouth, dizziness, blurred vision, constipation, hypotension, urinary retention, and bradycardia
Diltiazem[a]	30-60 mg by mouth 4 times daily	Diltiazem is a CYP450 3A4 moderate inhibitor – may increase risk of adverse effects of drugs that are CYP450 3A4 substrates Diltiazem is a CYP450 3A4 substrate – hypotensive effect can be exacerbated with concomitant use of CYP3A4 inhibitors	Avoid use in comorbid heart failure, as well as comorbid AV block, bradycardia, or other arrhythmia May cause AV block, bradycardia, and/or SJS/TEN	Peripheral edema, hypotension, tachycardia, headache, nausea, fatigue, and rash
Glycopyrrolate	1-4 mg by mouth twice daily	Avoid combining with medications that have anticholinergic activity because of increased risk of adverse effects	Use with caution in glaucoma, obstructive GI disease, and uropathy	Dry mouth, blurred vision, tachycardia, constipation, urinary retention, and memory impairment
Oxybutynin	2.5-5 mg by mouth twice daily	Avoid combining with medications that have anticholinergic activity because of increased risk of adverse effects	Use with caution in glaucoma obstructive GI disease, and uropathy	Dry mouth, blurred vision, tachycardia, constipation, urinary retention, and memory impairment
Propranolol[a]	5-20 mg by mouth 3 to 4 times daily	Propranolol is a CYP450 2D6/1A2/2C19 substrate – bradycardia and hypotensive effect can be exacerbated with concomitant use of a CYP450 2D6/1A2/2C19 inhibitors	Avoid use in comorbid respiratory disease (ie, asthma/COPD), AV block, and heart failure Use with caution in diabetes Withdrawal syndrome associated with abrupt discontinuation May cause or worsen bradycardia	Dizziness, drowsiness, fatigue, hypotension, bradycardia, cold extremities/Raynaud phenomenon, and erectile dysfunction

AV = atrioventricular; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CYP450 = cytochrome P450; GI = gastrointestinal; SJS = Stevens-Johnson syndrome; TEN = toxic dermal necrolysis.

[a]Available in immediate-release and extended-release formulations. Dosing is for immediate-release formulation.

suicidality. Her schizophrenia was resistant to treatment after adequate trials of oral second-generation antipsychotics. Both antipsychotic monotherapy and combination therapy were used with risperidone, olanzapine, and aripiprazole. Clozapine 400 mg/day produced an effective response but was accompanied by nocturnal generalized hyperhidrosis, sialorrhea, tachycardia, and significant worsening of constipation. She requested to discontinue clozapine because of these side effects. The hyperhidrosis was severe enough to require her to change her bed clothes during the night. There were no signs or symptoms of an infectious cause for hyperhidrosis including fever, cough, or upper respiratory symptoms. A complete blood cell count with differential was evaluated weekly because of the required risk evaluation and mitigation strategy for clozapine and showed no evidence of an infection. There was no suspicion or objective evidence of medication nonadherence, so cholinergic rebound as a cause of the hyperhidrosis was ruled out.

Additionally, she was not taking any other medications known to cause hyperhidrosis.

An oral anticholinergic medication was not initiated for hyperhidrosis because of a preexisting medical condition of inflammatory bowel disease and worsening constipation secondary to clozapine therapy requiring aggressive treatment with a bowel regimen. Based on a total clozapine level of 800 µg/L and tolerability issues, her clozapine dose was reduced by 50 mg/day, which did not decrease the hyperhidrosis. Propranolol 10 mg by mouth twice daily was added and titrated to 10 mg by mouth 3 times daily to target both hyperhidrosis and tachycardia. The beta-blocker was discontinued after 3 days because of worsening of asthma symptoms. The medical team was not aware of her medical history of asthma when initiating propranolol. Diltiazem CD 120 mg by mouth at bedtime was initiated and titrated to 180 mg/day, resulting in a prompt reduction (within 48 hours) in hyperhidrosis. Although complete resolution was not seen, treatment with the calcium channel blocker decreased the severity of hyperhidrosis. Diltiazem CD was well tolerated with no reported adverse effects or hypotension. She ultimately discontinued treatment of clozapine because of severe constipation and was started on a long-acting injectable formulation of aripiprazole. She did not report hyperhidrosis as a reason for wanting to discontinue clozapine. Diltiazem CD was also discontinued at this time. The hyperhidrosis resolved completely with clozapine discontinuation.

Discussion

Clozapine is most commonly used in treatment-refractory schizophrenia where management of side effects is important to ensure the patient can tolerate treatment. The sympathetic nervous system is responsible for initiating the sweat response when a thermal trigger causes acetylcholine to activate the sympathetic postganglionic fibers located within the hypothalamus.[6] The activation of this sympathetic response because of acetylcholine release sends a signal to increase intracellular calcium. Therefore, extracellular calcium moves into the intracellular space and induces the eccrine glands to actively secrete sweat.[6,7] Clozapine is a partial agonist at various muscarinic receptors (M_1, M_2, and M_3), thus causing an increase in acetylcholine release and triggering a larger sweat response.

Secondary generalized hyperhidrosis is most commonly treated with oral anticholinergic medications (eg, benztropine, oxybutynin, glycoyrrolate) as initial therapy. These medications act directly on the muscarinic receptor within the eccrine sweat gland to decrease sweating.[7] Use of a muscarinic antagonist to manage clozapine-induced hyperhidrosis can be problematic because of additive anticholinergic side effects. Propranolol, a nonselective beta blocker, and clonidine, an alpha-2 agonist, are treatment options that decrease sweating by reducing the activation of the sympathetic nervous system.[7] An alpha-2 agonist was not trialed in this patient because of concerns for additive side effects with clozapine such as dry mouth, drowsiness, dizziness, and constipation. Calcium channel blockers are generally reserved as last line following failed trials of anticholinergic agents, nonselective beta blockers, or alpha-2 agonists.[6,7] Use of a calcium channel blocker, such as diltiazem, to treat clozapine-induced hyperhidrosis renders calcium channels inactive. Blocking calcium channels prevents further calcium influx into the intracellular space, hence eccrine glands are not stimulated to release sweat.[6] The Table describes treatment options for clozapine-induced hyperhidrosis that have been noted in the literature.

Conclusion

This case report demonstrates the effectiveness of the calcium channel blocker diltiazem in reducing clozapine-induced hyperhidrosis. Use of nonselective beta blockers, alpha-2 agonists, and calcium channel blockers offer an alternative to anticholinergic medications for the treatment of hyperhidrosis that may negatively impact clozapine tolerability.

References

1. Clozaril [package insert]. Novartis Pharmaceutical Corporation; 2021.
2. Leung JG, de Leon J, Frye MA, Singh B, Cotes RO, McElroy SL. The modernization of clozapine. J Clin Psychopharmacol. 2022; 42(6):565-80. DOI: 10.1097/JCP.0000000000001606
3. Caulfield MP. Muscarinic receptors—Characterization, coupling and function. Pharmacol Ther. 1993;58(3):319-79. DOI: 10.1016/0163-7258(93)90027-B
4. Olianas MC, Maullu C, Onali P. Mixed agonist-antagonist properties of clozapine at different human cloned muscarinic receptor subtypes expressed in Chinese hamster ovary cells. Neuropsychopharmacology. 1999;20(3):263-70. DOI: 10.1016/S0893-133X(98)00048-7
5. Richardson C, Kelly DL, Conley RR. Biperiden for excessive sweating from clozapine. Am J Psychiatry. 2001;158(8):1329-30. DOI: 10.1176/appi.ajp.158.8.1329-a
6. Metzler-Wilson K, Wilson TE. Impact of calcium regulation on eccrine sweating and sweating disorders: the view from cells to glands to intact human skin. Exp Physiol. 2016;101(3):345-6. DOI: 10.1113/EP085639
7. Nawrocki S, Cha J. The etiology, diagnosis, and management of hyperhidrosis: A comprehensive review: Therapeutic options. J Am Acad Dermatol. 2019;81(3):669-80. DOI: 10.1016/j.jaad.2018.11.066