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An ulcerated mouth lesion following one dose of sublingual asenapine

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Abstract

Purpose: To report the first descriptive case of a mouth lesion following one dose of sublingually administered asenapine.

Summary: Asenapine is a second-generation antipsychotic, approved in the United States in August 2009, for the treatment of schizophrenia and acute mania associated with bipolar disorder. It is administered as a sublingual tablet to be taken twice daily. Although the mechanism of action has not been fully elucidated, it is thought to be mediated through a combination of antagonist activity at the dopamine and serotonin 5-HT2A receptors. Sublingual bioavailability is estimated at 35% and is highly plasma protein bound (95%). Oral administration results in low bioavailability (< 2%) due to extensive first-pass metabolism. Adverse tissue reactions identified by the manufacturer include mouth ulcers, blisters, and peeling/sloughing of the contact area. In one manufacturer-sponsored trial, oral paresthesia events were reported for the following administration routes: sublingual (75.8%), supralingual (55.9%), and buccal (45.7%).

Case Report: A 35-year-old patient diagnosed with schizophrenia and swallowing problems was on a regimen that included liquid haloperidol via oral syringe. Adherence was problematic and psychotic symptoms were poorly controlled. The patient was prescribed asenapine 5-mg sublingual tablets to be dissolved under the tongue twice daily. Following the first dose, the patient developed an extremely painful ulcerated lip lesion and refused additional doses. The Naranjo Probability Scale was applied and indicated a probable reaction (7 of 12).

Conclusions: In our patient, the adverse event occurred following one dose. Rechallenge was not attempted. Primary care providers may not be fully aware of the potential severity for this medication-related effect. Based on findings from the manufacturer, clinicians are encouraged to counsel patients and conduct follow-up to determine whether any adverse oral effects were experienced that might have an impact on medication adherence.

Keywords: asenapine, medication-induced oral blisters, mucosal lesion, oral lesion, sublingual

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Introduction

Asenapine is a second-generation antipsychotic (AP), approved in the United States in August 2009, for the treatment of schizophrenia and acute mania associated with bipolar disorder.[1] It is administered as a sublingual (SL) tablet to be taken twice a day. Although the mechanism of action has not been fully elucidated, it is thought to be mediated through a combination of antagonist activity at the dopamine (D2) and serotonin

5-HT2A receptors.[1] Sublingual bioavailability is estimated at 35% and is highly plasma protein bound (95%). Oral administration results in low bioavailability (<2%) due to extensive first-pass metabolism. Adverse tissue reactions identified by the manufacturer include mouth ulcers, blisters, and peeling and/or sloughing of the contact area. In one manufacturer-sponsored three-way crossover trial (n = 36), oral paresthesia (mild tingling or prickling feeling lasting for 10-30 minutes) events were reported for the following administration routes: SL (75.8%), supralingual (55.9%), and buccal (45.7%).[2] No information regarding the duration of use prior to the adverse event was included.

This case report will describe a patient who was prescribed asenapine SL tablets secondary to objective and subjective reports of psychosis and psychiatric instability. The patient experienced an ulcerated mouth lesion following the first dose. We reviewed the literature for reports of similar case reports as a potential consequence of AP use in patients similar to this patient. None were found. The Naranjo Probability Scale[3] was applied and indicated a probable causal relationship (7 of 12).

Case Report

The patient, a 35-year-old African American man diagnosed with schizophrenia and swallowing problems, received services provided by the Integrated Multidisciplinary Program of Assertive Community Treatment (IMPACT) team. Social history was positive for tobacco use with a two-pack-per-day history and no intention of quitting. He was able to live independently and manage his own finances, although supports were needed.

Problems with activities of daily living, such as an inability to maintain his apartment, were reported, and he demonstrated a high risk potential for homelessness because of an inability to pass housing inspections and complete the necessary paperwork required for supported housing.

The patient was medically stable. Annual baseline laboratory results for a comprehensive metabolic panel and complete blood count were within normal limits. More problematic was the potential for repeated psychiatric hospitalizations. Past medical history was significant for self-harm and assault secondary to auditory hallucinations. The patient was a poor historian with impaired insight regarding his illness.

In addition to housing and case management, medication therapy management was also provided by the IMPACT team. One component of the regimen included liquids self-administered via oral syringe. Despite home visits three times weekly to provide medication, assist with individual rehabilitation, and monitor medication use, medication adherence was problematic, and positive symptoms for psychosis, including paranoia and suspicion, were poorly controlled. A number of medication changes were made to stabilize the patient. The patient was prescribed asenapine 5-mg SL tablets to be dissolved under the tongue twice daily. The patient was also counseled to avoid drinking or eating for 10 minutes following use. Following use of the first dose, the patient developed an extremely painful ulcerated lesion on the inside margin of the lower lip and refused additional doses.

Asenapine was discontinued, and the lesion resolved without additional sequelae. Aripiprazole was initiated, with positive results evidenced by resolution of positive symptoms. The patient was lost to follow-up shortly afterward. Medication and adjustments are included in the Table.

Discussion

Asenapine is a novel psychopharmacologic agent that serves as both primary and adjunct therapy for acute treatment in adults with a diagnosis of schizophrenia, and as an effective adjunctive treatment for manic or mixed episodes associated with type 1 bipolar disorder with or without psychotic features. Asenapine belongs to a novel class of atypical AP compounds known as dibenzoxepinopyrrolidine derivatives and has a very distinct receptor-binding profile showing multireceptor antagonism at a combination of serotonergic, D2, α adrenergic, and histaminergic receptors while showing no appreciable binding at muscarinic or cholinergic receptor sites. Asenapine interactions with various subtypes of receptors, particularly serotonergic and D2 receptors, are being further explored for clinical significance. Studies suggest that its ability to bind with multiple receptor subtypes accounts for both its positive effects and its adverse outcomes. Binding affinity for D2 receptors is low when compared with other receptors. This greatly reduces the occurrence of extrapyramidal symptoms and hyperprolactinemia often associated with other atypical APs. Recent in vivo studies have also suggested that D2 antagonism can be a very significant component of clinical therapy.

The adverse effects that patients experience with asenapine are from inhibition of the same receptors that offer the negative symptom relief. Blockade of α_1 adrenoreceptors reduces negative symptomology in patients, but it also accounts for the orthostatic hypotension caused by the drug. Asenapine has no activity at muscarinic or cholinergic receptors, so there are neither the anticholin-

TABLE: Medications and adjustments

Drug	Dose	Changes	Outcome
Haloperidol decanoate, August 2012	150 mg IM every 4 weeks	Increased dose to 200 mg for next month	Increased to evaluate continued positive symptoms
Haloperidol decanoate, August 2012	200 mg IM every 4 weeks	Increased dose to 250 mg for next month	Increased to evaluate continued positive symptoms
Haloperidol decanoate, October 2012	250 mg IM every 4 weeks	Increased dose to 300 mg for next month	Increased to evaluate continued positive symptoms
Haloperidol decanoate, November 2012	300 mg IM every 4 weeks	None	Increased because of continued positive symptoms
Haloperidol liquid, August 2012	10 mg PO TID	None	Continued positive symptoms
Valproate acid liquid, August 2012	500 mg PO BID	HS dose increased to 1000 mg	Titration because of mood instability
Valproate acid liquid, September 2012	500 mg PO QAM 1000 mg PO QHS	HS dose increased to 2000 mg	Titration because of mood instability
Valproate acid liquid, June 2013	500 mg PO QAM 2000 mg PO QHS	None	Mood stabilization
Zolpidem	10 mg PO QHS	None	Better sleep reported
Propranolol, August 2012	10 mg PO BID	None	Anxiety
Asenapine, June 2013	5-mg SL BID		Discontinued after first dose following ulceration
Aripiprazole, June 2013	20-mg orally disintegrating tablet daily	Dosage reduction requested because of continued sedation and poor quality of life	Resolution of positive symptoms
Aripiprazole, September 2013	10-mg orally disintegrating tablet QHS	None	Resolution of excessive sedation

BID = twice a day; IM = intramuscular; PO = orally; QAM = every day before noon; QHS = every night at bedtime; SL = sublingual; TID = three times a day.

ergic effects nor the metabolic syndrome issues that are commonly associated with other second-generation APs. It is also an antagonist of the H1 histamine receptor, which led developers to suspect that asenapine would cause both sedation and weight gain. This was later proven true by researchers during clinical trials.[4]

Although the anticipated profile for asenapine relates to its receptor profile, SL administration may result in oral hypoesthesia (numbness). Based on use during acute treatment of up to 6 weeks in patients with a diagnosis of schizophrenia, information from the manufacturer reported that the incidence of oral hypoesthesia was 6% (n = 274) with use of 5 mg administered twice daily, and 7% (n = 208) with the 10-mg SL tablet administered twice daily, compared with 1% for placebo (n = 378). The incidence was 5% with flexible dosing (n = 572).[5] Results from the 3-week bipolar mania trial reported the incidence was less than 1% with placebo (n = 203) and 4% with flexible dosing of 5 or 10 mg used twice daily.[5]

In comparison trials of asenapine and placebo, olanzapine, and haloperidol, rates were 5% compared with 0.7%, 0.3%, and 0%, respectively. Although the exact mechanism is not known, the manufacturer theorizes it is secondary to a local anesthetic effect.[6]

Conclusion

In our patient, the adverse event occurred following one dose. Rechallenge was not attempted. Primary care providers may not be fully aware of the potential severity for this medication-related effect. Based on findings from the manufacturer, clinicians are encouraged to counsel patients and conduct follow-up to determine whether any adverse oral effects were experienced that might have an impact on medication adherence.

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