Aspiration Pneumonia Due to Clozapine-Induced Sialorrhea

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Introduction

Clozapine is a second-generation antipsychotic, which use is limited to treatment-resistant cases of schizophrenia. Sialorrhea, a well-known side effect of clozapine, occurs in 31–54% of patients receiving clozapine therapy (1). Patients may complain of both daytime and nighttime drooling (the "wet pillow" sign). Here, we report the case of a young man who developed aspiration pneumonia due to clozapine-induced sialorrhea.

Case Report

Mr. C, a 26-year-old male with schizophrenia paranoid type and a long history of numerous psychiatric hospitalizations, was admitted to our inpatient unit for treatment of difficulty sleeping, paranoia, auditory hallucinations and inability to function following non-compliance with his medication (risperidone). His medical history was unremarkable. Complete blood count, basic metabolic panel, and thyroid stimulating hormone levels were within normal limits. On our inpatient unit, he was found to be irritable, guarded, internally preoccupied, gesturing and talking to himself. His past psychiatric history was significant for failure to respond to multiple typical and atypical antipsychotics (chlorpromazine, fluphenazine, perphenazine, quetiapine, olanzapine, aripiprazole, ziprazidone). He had partial response to risperidone, described by his outpatient psychiatrist as moderate reduction of paranoia and hallucination. Mr. C was restarted on risperidone which was titrated up to 4 mg twice a day. He remained paranoid, disorganized with auditory hallucinations telling him that he was the son of a famous singer. On Day 10 of admission, haloperidol was added and titrated up to 10 mg bid.

Despite being on two antipsychotics for more than three weeks, Mr. C did not improve and the decision was made to discontinue risperidone, haloperidol and start clozapine. After initiation of clozapine to 75 mg orally daily (the patient was started on 12.5 mg per day, gradually increased to 75 mg per day), Mr. C experienced side effects from the medication, including severe sialorrhea, sedation, headache and tachycardia. The sialorrhea was present both during the daytime and nighttime; the patient said that the sialorrhea was more bothersome during the nighttime. The patient was seen wearing a towel around his neck that he used to wipe his mouth.

On Day 5 after initiating clozapine, the patient spiked a fever of 103° F and developed altered mental status with difficulty breathing. He was transferred to the emergency room where findings on physical examination and radiographic evidence of an infiltrate lead to a diagnosis of pneumonia. Further investigations revealed a positive sputum culture for peptostreptococcus as the causative organism. The source of pneumonia was deemed to be aspiration. He underwent antimicrobial therapy of ceftriaxone and fluoroquinolone; clozapine was discontinued. After five days of antimicrobial therapy, Mr. C was readmitted to the psychiatric unit where

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he continued his course of antimicrobial therapy and haloperidol was reinstated, titrated up to 20 mg bid over a two-week period. His psychotic symptoms marginally improved; on day of discharge, Mr. C reported a diminution of auditory hallucinations and appeared less paranoid. He did not experience any extrapyramidal or significant side effects to the medication.

Clinicians should keep in mind that aspiration pneumonia is one of the more serious complications of clozapine treatment.

Discussion

Mr. C developed fever, tachycardia, and sedation in the setting of clozapine titration. The differential diagnosis for such a presentation is broad and includes neuroleptic malignant syndrome, myocarditis, agranulocytosis-related infection, or simply temporary side effects of clozapine. As our case illustrates, clinical suspicion for aspiration pneumonia as a result of clozapine-induced sialorrhea was low. Patients may complain of both daytime and nighttime drooling (the "wet pillow" sign). Some describe a choking sensation that keeps them awake at night (1). Sialorrhea usually develops early in treatment with clozapine and may be associated with rapid dose titration (2). Clozapine-induced sialorrhea is counter-intuitive given that clozapine is the most anticholinergic of all the antipsychotics and would be expected to cause a dry mouth (3). In-vitro studies have shown that clozapine acts antagonistically on multiple receptor systems, but has an agonist effect on both the M4 muscarinic receptors and sympathetic alpha-2 adrenoceptors in the acinar cells of the salivary glands, which may lead to increased saliva secretion. However, salivary flow studies comparing patients with sialorrhea to controls have not shown a significant difference in salivary flow rate, prompting some to argue that clozapine interferes with the swallowing function (possibly an antidopaminergic effect) that then results in pooling of saliva (4).

Aspiration pneumonia associated with clozapine use is not well documented. A recent PubMed search revealed only one documented case of aspiration pneumonia in a patient on clozapine who developed profuse salivation (5). The commonly cited risk factors for developing aspiration pneumonia include dysphagia, esophageal dysfunction, impairment of consciousness, and increased bacterial inoculum (6). In fact, one large clinical study reported respiratory infections to be the most common single cause of death in patients on clozapine (7). It is noteworthy that none of the patients who developed pneumonia while on clozapine had neutropenia or leukopenia (8).

Sialorrhea likely contributed to aspiration pneumonia in our patient. One day after he was noted to have profuse salivation, Mr. C developed pyrexia. The time course is highly suggestive of aspiration pneumonia, which was confirmed by chest x-ray and sputum culture. Our patient may have warranted more aggressive treatment when he first developed sialorrhea. Patients who develop sialorrhea in the hospital are not routinely placed on aspiration precautions, but our patient might have benefited from such an intervention. Sialorrhea is difficult to treat but does not necessarily require discontinuation of clozapine. Management of sialorrhea is both behavioral (encouraging swallowing, chewing gum, elevating the head at night with pillows, maintaining a lateral decubitus position) and pharmacological (alpha-2 agonists such as clonidine, anticholinergic agents such as atropine drops, or ipratropium nasal spray) (9).

Clozapine-associated aspiration pneumonia is a multi-factorial process that may involve any or all of the following: sialorrhea, increased sedation, potential esophageal dysfunction, and a pre-disposition to aspiration among psychiatric patients.

Clinicians should keep in mind that aspiration pneumonia is one of the more serious complications of clozapine treatment. Clozapine-associated aspiration pneumonia is a multi-factorial process that may involve any or all of the following: sialorrhea, increased sedation, potential esophageal dysfunction, and a pre-disposition to aspiration among psychiatric patients. Complaints of difficulty swallowing, choking, and weight loss (even in the absence of sialorrhea) prompt special attention to esophageal dysfunction (10). Because any bronchial infection (and the antibiotics used to treat such infections) can elevate clozapine levels through inhibition of the hepatic cytochrome P450 1A2 that metabolizes clozapine, it is important to simultaneously monitor for clozapine toxicity (11). It may be necessary to decrease the dose of clozapine, or even discontinue the medication in some individuals.

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