[CASE REPORT]

Pseudoephedrine for the Treatment of Clozapine-Induced Incontinence

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ABSTRACT

Clozapine, the first atypical antipsychotic, is well known for superior efficacy in the treatment of refractory schizophrenia. Though the side effect most often associated with clozapine is the potential for causing blood dyscrasias, other lesser known side effects, including clozapine-induced incontinence, may result in the unnecessary discontinuation of this essential psychiatric medication in patients who otherwise have no alternative to treatment. Here we describe a case of pseudoephedrine used successfully as a therapeutic intervention for clozapine-induced incontinence.

INTRODUCTION

Clozapine, an atypical antipsychotic, is indicated for the management of severe schizophrenia.[1] It exhibits its effects through antagonism at dopaminergic, serotonergic, adrenergic, cholinergic, and histaminergic receptors. Common side effects reported with the use of this medication include sedation, dizziness, tremor, headache, constipation, hypersalivation, tachycardia, and syncope. Another lesser known side effect that has been more recently reported in studies is urinary incontinence. In fact, it has been estimated that anywhere between 1 to 42 percent of patients suffer from this condition.[2] While clozapine-induced urinary incontinence can be treated by decreasing the dose or switching to an agent with less anticholinergic activity, for many patients, clozapine is the only antipsychotic that can effectively treat their schizophrenia.[3] Therefore, treatment options for clozapine-induced urinary incontinence are essential. In contrast to typical incontinence treatment agents, the use of ephedrine has been shown to be effective in clozapine-induced incontinence.[4] We report a case of clozapine-induced incontinence treated with pseudoephedrine.

CASE REPORT

In February of 2010, a 58-year-old man diagnosed with schizophrenia, paranoid type, was hospitalized in a state psychiatric facility. His medical history was significant for cardiopulmonary disease (COPD), hepatitis B, hepatitis C, gastroesophageal reflux disease (GERD), and substance abuse. His past substance abuse resulted in ataxia and limited mobility, requiring wheelchair assistance. This patient also had numerous prior admissions and was treated with multiple trials of typical and atypical antipsychotics, mood stabilizers, antidepressants, and anxiolytics; however, his psychiatric illness remained unstable

and refractory. In February of 2010, the patient was initiated on clozapine with vigilant titration and monitoring of white blood cells and absolute neutrophil count. The patient's lab work remained within normal range and his psychotic symptoms improved during treatment. Soon after initiating clozapine therapy, the patient became incontinent. He had to wear adult incontinence pads as well as make use of a bedside urinal, which became a barrier to his ultimate discharge from the facility.

On April 3, 2012, the patient agreed to the doctor's recommendation of pseudoephedrine 30mg four times a day. Just three days after initiation of pseudoephedrine, the staff at the facility began reporting that the patient remained continent overnight. The staff denied any reports of spilled urine or enuresis for the entire month of April. Other therapeutic factors may have contributed to the increased level of continence, such as scheduled toileting; however, to the present day the patient continues to remain continent. The initiation of clozapine reduced his psychotic symptoms such that the patient infrequently mentioned delusions. With such improvements in mental and physical health, the patient is hoping to be discharged from the facility very soon.

DISCUSSION

Urinary continence requires a delicate balance between urethral closure and detrusor muscle activity.[5] Abnormalities of the urethra and bladder result in the involuntary leakage of urine, known as urinary incontinence. Clozapine-induced urinary incontinence often presents as nocturnal enuresis.[2] While it generally develops within the first few days after initiation of therapy, it can occur weeks or months later. For some patients, this incontinence can be transient during early therapy; however, for others it can persist throughout their treatment duration on clozapine therapy.[6] The mechanism by which clozapine induces urinary incontinence is believed to be multifactorial.[4] Through its potent antiadrenergic activity, clozapine could potentially reduce the bladder tone of the internal sphincter. Overflow incontinence can occur too as a result of urinary retention through clozapine's antagonism at muscarinic receptors.[7] Clozapine also affects central mechanisms in urinary incontinence. As an antagonist at 5-HT_{2A} and 5-HT_{2C} receptors, clozapine blocks the inhibitory effects of the 5-HT_2 receptors on the parasympathetic neurons that innervate the bladder.[8] Clozapine is also an agonist at the 5-HT_{1A} receptor, which stimulates the micturition reflex.[9] In addition, it has been proposed that by acting as an antagonist at dopamine D_1–D_5, clozapine produces a hypodopaminergic state that may induce bladder hyperactivity.[10] Additional clozapine side effects that could contribute further to an incontinent state include sedation and lowering of the seizure threshold.[11]

The superiority of clozapine as a treatment intervention for schizophrenia has been well documented, and thus discontinuation or dose reduction is often not the best treatment option for patients. In the case of this patient, clozapine substantially improved his quality of life; however, soon after initiation, the patient began to experience urinary incontinence. While antimuscarinics, such as oxybutynin, can be effective in managing incontinence, for some patients it is intolerable and ineffective.[12] In this patient, the role pseudoephedrine can play in incontinence treatment is revealed.

The study that demonstrated the effectiveness of ephedrine as a therapeutic option for clozapine-induced incontinence resulted in our exploration of pseudoephedrine as an alternative.[4] Ephedrine, an alpha-adrenergic agonist, was believed by Fuller et al[4] to reduce clozapine's potent antagonism at alpha-adrenergic receptors thereby increasing bladder tone. To test their theory, Fuller et al studied a total of 57 patients diagnosed with schizophrenia who were newly started on clozapine therapy. Patients that developed clozapine-induced urinary incontinence were treated with ephedrine. The dose was increased until resolution of incontinence was achieved or the maximum dosage of 150mg/day was reached. Of the 16 patients who developed urinary incontinence and were treated with ephedrine, 15 showed improvement after receiving the maximum dosage. Twelve patients had complete resolution of their symptoms, three patients had reduced frequency, and one had no response to treatment. Ephedrine did not alter mental status in these patients or reveal any major side effects. Such success rates with ephedrine reveal that clozapine's antagonism at the alpha-adrenergic receptors may be one of the main causes of urinary incontinence.

The use of pseudoephedrine, also an alpha-adrenergic agonist, is an additional choice for the treatment of clozapine-induced urinary incontinence.[12] When alpha-adrenergic receptors are activated, the smooth muscles of the bladder contract, increasing urethral closure pressure and helping to maintain continence. Pseudoephedrine 30mg four times a day led to remission of our patient's symptoms as he continues to remain continent to the current day. With his improvements in mental health and physical health, he is expected to leave the facility soon. Our review of the literature did not result in any studies of pseudoephedrine for the treatment of clozapine-induced urinary incontinence; however, there are studies on pseudoephedrine for incontinence in general.[12,13] Our case report and supporting literature reveal that pseudoephedrine could be a suitable treatment option for clozapine-induced urinary incontinence for many patients.

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