Rapid Resolution of Psychotic Symptoms in a Patient with Schizophrenia Using Allopurinol as an Adjuvant: A Case Report

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Abstract

Context: Despite multiple trials of different adjuvant therapies to an antipsychotic regimen, there have been few promising results. Allopurinol may be one promising adjunctive therapy based on three randomized controlled trials. **Objective:** To determine whether adjuvant allopurinol would be beneficial to a patient already on multiple trials of antipsychotics with no improvement. **Results:** Allopurinol was started with this particular patient who was on the inpatient unit for over three months with no prior improvement. Within two weeks of allopurinol adjuvant therapy, the patient showed significant improvement with regards to his positive and negative symptoms of schizophrenia (PANSS scores went from a score of 88 to a score of 41 two weeks later). **Conclusions:** Despite some limitations of this particular case report, it is possible that allopurinol can play an effective role as an adjuvant to antipsychotic regimens in reducing the symptoms of schizophrenia.

Key Words: Allopurinol, Schizophrenia

Introduction

Schizophrenia is a major psychotic disorder that is chronic in nature with multiple relapses, even when treated appropriately with medications (1, 2). Antipsychotics are the mainstay treatment for the positive symptoms of schizophrenia. It is believed that neurotransmitters play an important role in the pathophysiology of schizophrenia. The dopamine hypothesis has been the most prolifically supported theory. It has been found that D2 blockade is required for the antipsychotic action of this drug class (2). However, with the advent of second-generation (atypical) antipsychotics, other receptors have been implicated, such as serotonergic, cholinergic, glutamatergic, and GABAergic (2).

Adjuvant treatments that augment traditional antipsychotics are currently being investigated. One such adjuvant that has shown success in early studies is allopurinol, a xanthine oxidase inhibitor used to treat hyperuricemia and gout. Lara et al. proposed that adenosine is a contributor to the pathophysiology of schizophrenia via the adenosine dysfunction hypothesis, which implicates adenosine as a factor in modulating dopamine and glutamate (3). Increased adenosinergic transmission is thought to decrease the affinity of dopamine agonists for dopamine receptors. Ferre showed that adenosine agonists antagonize the activity of dopamine in the ventral striatum of the brain; thus, adenosine agonists, such as allopurinol, show similar results to dopamine antagonists, such as antipsychotic medications (4).

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To date, there have been two case reports from an observational study (5), one independent case report (6), two randomized, double-blind, placebo-controlled trials, and one randomized, double-blind, placebo-controlled, crossover trial to test this hypothesis (7-9). In 2005, Akhonzadeh et al. enrolled forty-six inpatients with acute schizophrenia to a regimen of 300 mg of allopurinol per day in addition to their antipsychotic regimen. Four weeks later, compared with controls, those in the allopurinol group showed significant improvement in scores based on the Positive and Negative Syndrome Scale (PANSS) (7). In 2005, Brunstein et al. conducted a randomized, double-blind, placebo-controlled, crossover trial in which thirty-five inpatients and outpatients with refractory schizophrenia received 300 mg of allopurinol twice daily in addition to their antipsychotic regimen. Among the twenty-two patients that completed the study (after another six weeks of crossover), there was again a significant improvement in the PANSS scores from baseline (8). Dickerson et al. randomly assigned fifty-nine outpatients with moderately severe schizophrenia (based on baseline PANSS scores) to receive adjunctive allopurinol 300 mg twice a day versus placebo. Among the fifty-one completers of the trial, four out of thirty-one in the allopurinol group and zero of twenty-eight in the placebo group had at least a 20% reduction in total PANSS score (9). These studies were limited by their small sample sizes, trial length (the longest was eight weeks), and the Brunstein crossover study had a high drop-out rate (2). Yet, all three studies show the benefit, albeit modest, of adding allopurinol as a safe adjunct to an antipsychotic regimen for those patients who have not had success in their previous antipsychotic treatment (2, 7).

Case Report

The following case discussion describes a 44-year-old African male who was an inpatient for over four months, with multiple trials of antipsychotics, who eventually showed significant improvement when allopurinol was added as an adjunct to his antipsychotic regimen. This abstract will focus on his psychopharmacological treatment regime as related to his eventual improvement.

The patient was a middle-aged African male who arrived at the psychiatric emergency room of our hospital by emergency petition on the order of the police, after he was found walking naked in front of a court house. The patient did not have any identification with him, and he was not able to answer any questions except that his name was "Onassis" and that he was from heaven. Other than the fact that the patient stated later that he was from Lagos, Nigeria, he was, in general, selectively mute with the treatment team, except for a few words to describe his symptoms. Usually, the patient would just respond that he heard "voices" and that he felt "sad" due to the voices. He was also sometimes seen responding to internal stimuli, and he endorsed bizarre delusions, such as the belief that the outside world was "heaven" or that it was "Lagos." Sometimes, the patient stated that he saw "snakes" and that he had "snake blood." Otherwise, the patient was completely isolative, demonstrated poor hygiene and overall self-care, did not participate in the milieu, and was only poorly interactive with the treatment team. He showed positive (hallucinations, delusions) and negative (alogia, asociality, avolition, flat affect) symptoms of schizophrenia.

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The patient had the requisite laboratory studies drawn, as well as a computed tomography (CT) scan of the brain to rule out any evidence of structural central nervous system abnormalities. His laboratory panel was unremarkable and CT imaging was negative for acute and chronic pathology. It was unclear if the patient had a substantial drug history or a history of any neurological disorders, such as epilepsy.

To sum up the patient's psychopharmacological regimen during his first two months on the unit, the patient took haloperidol, lorazepam, benztropine, olanzapine, risperidone, ziprasidone, chlorpromazine, lithium, valproic acid, and fluoxetine at different times in varying combinations and titrations. The pharmacologic criterion for treatment refractoriness has been defined as three reasonably long trials of antipsychotics in different chemical classes (at dosages that are at least equivalent to 1,000 mg of chlorpromazine) that have been administered at steady-state levels over a period of six weeks with no symptomatic relief (10). With the exception of valproic acid, all of the antipsychotics and mood stabilizers were at dosages that would be considered sufficient for treatment of schizophrenia and mood disorder. Further, each antipsychotic trial length (within the combinations) was at least one week and at longest, four weeks. The numerous medication combinations were based on behavioral changes (or sometimes lack thereof) in the milieu. While it cannot be said that the patient was truly "treatment refractory," there was a clear pattern of lack of response to what would be generally effective treatments for generally effective durations.

After nearly two months of trying the above medications in different regimens and combinations without improvement, it was decided that the patient would benefit from a clozapine trial. At this point, the patient was also

taking ziprasidone, fluoxetine and lorazepam. However, after one week on clozapine, the patient had his weekly complete blood cell count drawn and it was discovered that his absolute neutrophil count (ANC) had decreased by more than half (3.4/mm^3 to 1.3/mm^3). The patient also stated that he felt "sick," so clozapine was immediately discontinued. Within one week, his absolute neutrophil count was back to a safer level above 1.5/mm^3. After this trial, a decision was made to start paliperidone while tapering ziprasidone. After nearly two weeks on this medication with no improvement, an attempt to add loxapine was made. However, again, the patient's absolute neutrophil count showed a concerning decrease over several days, so this was discontinued as well. Thereafter, the patient had daily complete blood counts drawn with differentials; his ANC fluctuated, but never dropped below 0.9/mm^3 and it normalized in seven days.

The patient continued on paliperidone for the next two weeks (titrated up to 12 mg daily), and he also continued to receive fluoxetine 40 mg daily. However, he continued to endorse hallucinations, was delusional, and continued to decline to participate in the milieu or interact with others. After reading some of the literature concerning allopurinol as an adjuvant, it was decided that this should be undertaken with the hope of symptomatic improvement. The patient was started on allopurinol 300 mg twice daily. His baseline PANSS scores calculated the day allopurinol therapy commenced was 88. This was quite high compared with the sample of patients in the controlled studies relating to the use of allopurinol. However, within a week, the patient began to show improvement, and within two weeks the results were quite striking. He began to tell the treatment team that he did not hear "voices," that he was no longer "sad" because the voices were gone, that he did not see "snakes," and that he knew that he was in Baltimore, Maryland. Soon thereafter, he wanted to know when he could be discharged, something he had never mentioned in the past. He also reported improved sleep and his activities of daily living (ADLs) improved: previously, the patient had sported a heavy, unkempt beard but, by the end of the hospital stay, he had shaved his beard and had a trim moustache. The patient began to initiate attendance at occupational therapy groups on his own, and even participated during the activity groups, much to the surprise of the staff who had previously been unable to even coax the patient to go to any of the workshops. Two weeks after starting the allopurinol as an adjunctive treatment, his PANSS score had decreased to 41. Allopurinol was well-tolerated and the patient did not endorse any of the side effects often associated with this medication, including dermatologic or gastrointestinal side effects. He was able to participate in discharge planning with the team, and he was subsequently discharged to outpatient care.

Conclusions

The purpose of this case report is to further support previous positive studies with regard to the addition of allopurinol as an adjunct to antipsychotic medications. There are several weaknesses in this case study, however. First, the patient had almost one month of paliperidone therapy before starting allopurinol as an adjunct. It is difficult to conclude whether his overall improvement was due to the extended use of paliperidone (at the highest recommended dosage), the additive effects of the previous antipsychotic trials, or due to the addition of allopurinol. With regard to the previous controlled trials, the PANSS scores decreased modestly in the Dickenson et al. and Brunstein et al. studies, and more dramatically in the Akhondzadeh et al. study (7-9). However, even in the Akhondzadeh study, the decrease in PANSS scores occurred over an eight-week interval (7).

However, these early clinical trials and case reports have shown that it is possible that allopurinol can reduce positive and negative symptoms in patients with schizophrenia who are achieving only a suboptimal response with traditional antipsychotic therapies.

In this case report, the patient experienced a dramatic improvement within two weeks of starting allopurinol, and this improvement was maintained until discharge from the inpatient unit. Yet, Lara et al. reported a 27-point decrease in PANSS scores over a three-week period for a patient started on adjunctive allopurinol (5). The idea of a "delayed onset" of antipsychotic response has been challenged and it has been posited that the most robust response to antipsychotics would be seen in the first two weeks than in any other period (11). Considering this patient was on paliperidone for three weeks with no improvement, as well as several D2 blockers before that, it is less likely that paliperidone or any other antipsychotics were the cause of his improvement. Further, given his sensitivity to certain medications such as clozapine and loxapine, it can be posited that the patient responded quite strongly to certain medications, and that perhaps this patient had an uncharacteristically robust response to allopurinol, which accounted for his significant and rapid improvement. As there have been no studies assessing the efficacy of allopurinol when added to clozapine, this would have been the first such reported case (2). Unfortunately, the patient became neutropenic on clozapine less than one week after starting it.

Another weakness was that the PANSS scoring was not performed in a blinded manner, and some rater bias might

have been unintentionally introduced into this assessment. More clinical trials with larger sample populations and for longer periods need to be done before allopurinol can be prescribed as a routine adjuvant therapy in patients with refractory schizophrenia (2). However, these early clinical trials and case reports have shown that it is possible that allopurinol can reduce positive and negative symptoms in patients with schizophrenia who are achieving only a suboptimal response with traditional antipsychotic therapies.

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