Case Report: The clinical implications of clozapine and cigarette smoking

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INTRODUCTION

Cigarette smoking is prevalent among psychiatric patients, with rates several times higher than the general population. As an example, up to 80% of schizophrenic patients smoke cigarettes.[1] Clozapine is extensively metabolized by cytochrome P450 isoenzyme 1A2 and polycyclic aromatic hydrocarbons (PAHs) present in cigarette smoke are thought to induce CYP 1A2.[1,2] Therefore concurrent smoking with clozapine can potentially lead to decreased clozapine levels and decreased efficacy, while smoking cessation can potentially lead to increased levels and toxicity. Enzyme induction has been reported to result in a 20 to 40% lower mean clozapine concentration in smokers compared to nonsmokers.[2] We present a case of altered serum drug concentrations in association with changes in smoking status in a patient upon admission to a nonsmoking inpatient psychiatric facility.

CASE SUMMARY

IR is a 33 year old white male brought by emergency medical services (EMS) to the emergency department with psychotic symptoms and anxiety and was admitted to a nonsmoking inpatient psychiatric facility the following evening. Past medical history was significant for chronic schizophrenia and obesity. The patient's age at onset of psychotic symptoms and full treatment history were unknown, although he had a history of multiple psychiatric hospitalizations. The patient was unemployed and living in a group home. He had decompensated during the week prior to admission with increasing auditory and visual hallucinations and paranoia. Medications prior to admission consisted of clozapine 700 mg PO every night at bedtime, paliperidone 6 mg PO twice daily, and trifluoperazine 10 mg PO every night at bedtime. IR had been compliant with hematologic monitoring with clozapine, and was known to have been on clozapine for greater than one year based on monthly hematologic monitoring. According to the patient and his mother, he had been compliant with medications prior to admission. Social history was significant for smoking one pack of cigarettes daily, occasional alcohol use, and no other substance use. On admission IR was noted to have tachycardia (HR 119 bpm) and a BMI of 31 (obese); all other labs and vital signs were within normal limits.

On admission, the patient reported auditory hallucinations, paranoid delusions, and persecutory delusions, with voices saying they were going to kill him. IR was known to respond to internal stimuli and report invisible people assaulting him at baseline, and these thoughts and beliefs never completely resolved even with significant doses of antipsychotics. He normally attended to activities of daily living (ADLs) with prompting but was not attending to ADLs at all at the time of admission. He denied suicidal or homicidal ideation. He appeared withdrawn and isolative, and had increased latency and poverty of speech. He displayed dysphoric mood, flat affect, thought blocking, and limited insight and judgment. IR was initially restarted on home doses of clozapine, paliperidone, and trifluoperazine.

On Day 2, the patient reported dizziness on standing. A clozapine level was ordered and orthostatic vital signs were monitored due to questioned compliance with clozapine before admission and suspected clozapine-induced orthostatic hypotension and tachycardia with the 700 mg dose. The patient displayed orthostatic hypotension and tachycardia for several days, but a bad sample was taken for the clozapine level. Negative cardiac enzymes and an EKG showing sinus tachycardia were thought to rule out clozapine myocarditis. On Day 4 the potential interaction between clozapine and cigarette smoking was identified and the dose of clozapine was decreased to 200 mg every morning and 300 mg at bedtime. On Day 11 the dose of clozapine was further

decreased to 125 mg every morning and 300 mg at bedtime, and propranolol 10 mg PO three times daily was initiated for clozapine-induced tachycardia. The hypotension and tachycardia gradually improved and was thought to be resolved by Day 17 of admission, however a clozapine concentration on that day was 767 ng/mL (therapeutic concentration typically thought to be 200 to 700 ng/mL). Several additional adjustments to IR's medication regimen occurred throughout the clinical course including addition of divalproex sodium on Day 4 and addition of memantine on Day 11 for clozapine augmentation.

IR showed gradual clinical improvements through the clinical course including reported decrease in auditory hallucinations, improvement in ADLs with prompting, decreased isolation and increased spontaneous speech. However, he continued to display significant negative symptoms. Of note, IR had continually asked throughout the course if he could smoke, and smiled for the first time on the day of discharge because he could smoke cigarettes again. Taking into consideration resumption of smoking on discharge, the patient was discharged on Day 18 on a clozapine titration consisting of 425 mg daily dose for 4 days, then 500 mg daily dose for 7 days, then 600 mg daily dose. The patient was also discharged on divalproex 1500 mg PO at bedtime, paliperidone 12 mg PO daily, memantine titration to 10 mg PO twice daily, and propranolol 10 mg PO three times daily.

COMMENT

Discontinuation of smoking at previously tolerated daily doses of clozapine has been reported to lead to clinically dangerous toxic effects. Again, the mechanism of this interaction is thought to be due to induction of metabolism of clozapine through CYP 1A2 by compounds in cigarette smoke. With smoking cessation this induction ceases and increases in clozapine concentrations may be seen. One case report describes tonic-clonic seizures, stupor and coma after abrupt smoking cessation in a chronic heavy smoker stabilized on clozapine 700-725 mg for greater than seven years. The patient recovered and clozapine was initiated at 40% of the original dose based on several random adjustments until the patient was clinically well.[3] The onset of decreased CYP 1A2 activity after smoking cessation varies from days to weeks in the literature. Faber and colleagues demonstrated a half-life of 1A2 decrease of 38.6 hours, with a decrease present in all subjects by day six after smoking cessation in twelve patients smoking 20 or more cigarettes daily. A new steady state was reached after around one week. This study used a paraxanthene to caffeine ratio (caffeine is often used as a marker of 1A2 activity).[2] Meyer and colleagues found a mean increase of 71.9% in clozapine levels after smoking cessation in eleven patients on stable clozapine doses after a minimum of two weeks.[4] Recommendations for dose adjustment in clozapine after smoking cessation also vary widely. Recommendations based on two studies published in 2004 consist of decreasing clozapine dose either 40% or 1.5 fold. The Faber study recommended reduction in clozapine dose immediately upon cessation of heavy smoking. A daily dose reduction of 10% per day for 4 days accompanied by therapeutic drug monitoring was the proposed strategy for dose adjustment.[2] Meyer and colleagues developed a linear predictive model for changes in clozapine level with smoking cessation explaining 80.9% of changes in clozapine levels upon smoking cessation, demonstrating that clozapine dose and serum concentration have a linear relationship. This is relevant for patients with a baseline clozapine level between 261 and 713 ng/mL.[4] Finally, in a study evaluating the influence of dose, cigarette smoking, age, sex and metabolic activity on plasma concentrations, clozapine and norclozapine assays were conducted in 3782 patients. Predicted plasma clozapine concentrations were found to increase 48% in nonsmokers and resulted in a recommended reduction of 1.5 fold in clozapine dose after smoking cessation.[5]

With resumption of smoking, induction of clozapine metabolism by CYP1A2 may be seen, leading to a decrease in clozapine concentration. Several weeks are required to see maximal effects of inducers due to the requirement for synthesis of new enzymes.[6] With resumption of smoking greater than one pack per day, one recommendation involves increasing clozapine dose by a factor of 1.5 over 2 to 4 weeks, with close monitoring of clozapine concentrations and adverse effects because the 1.5 factor is a gross approximation.[6]

A predicted clozapine level after smoking cessation could not be calculated for IR using the Meyer equation because a baseline level was not obtained. Results for the initial clozapine concentration did not come back for about a week and the sample was clotted. However, on a previous admission the patient had a clozapine level of 689 ng/mL on a total daily dose of 500 mg after six days of smoking cessation. Using this level as a nonsmoking level, this would predict a level of 436 ng/mL at baseline, however this information could not be applied to dosing recommendations during this admission. Based on the linear relationship demonstrated by Meyer and colleagues, a 40% decrease in dose should correlate with a 40% decrease in clozapine serum concentration. The

dose of IR's clozapine was ultimately decreased by around 40% from 700 mg to 425 mg total daily dose based on the recommendation by Faber and colleagues. Alternatively, following a recommended reduction of 1.5 fold in clozapine dose would have correlated to a decrease in clozapine dose to 350 mg for IR. The clozapine dose likely could have been decreased further than the decrease to 425 mg daily, however at the time of these adjustments clozapine concentration results were pending, and there are conflicting recommendations for the optimal approach to dose adjustment as stated previously. When IR was discharged home, the clozapine dose was not immediately increased and was not titrated back to his preadmission dose due to the supratherapeutic concentration prior to discharge. The therapeutic range of clozapine is generally thought to be 200 to 700 ng/mL, and with concentrations greater than 700 ng/mL no greater benefit but greater toxicity is seen. However, the patient did not have follow-up for several weeks at discharge and it was felt that the clozapine dosing needed to be addressed due to the risk of the clozapine concentration decreasing with resumption of smoking. Based on an expected baseline concentration of 436 ng/mL with a measured nonsmoking level of 689 ng/mL from the patient's previous admission, a concentration less than 700 ng/mL would be expected with a total daily dose of 600 mg.

To conclude, there is a significant interaction between clozapine and cigarette smoking due to cytochrome P450 1A2 although clinical data regarding the nature and management of this interaction are extremely limited and inconsistent and further studies regarding this interaction are needed. Based on available data it appears that an immediate dose reduction of 40% upon smoking cessation may be effective to maintain clozapine concentration within the therapeutic range. Recommendations for increasing the dose upon reinitiation of smoking are based upon clinical judgment. It appears that resuming the dose prior to smoking cessation over a period of 2 to 4 weeks may be reasonable.

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