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Case Report

A Case of Olanzapine Resistance from Heavy Smoking and Clinical Considerations

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INTRODUCTION

Cytochrome P450 (CYP) enzymes play a critical role in the metabolism of numerous drugs. Substances that inhibit or induce CYP enzymes can lead to suboptimal medication responses or toxicity.[1] Olanzapine, a second-generation antipsychotic, is widely used to manage various psychiatric disorders.[2] Its mechanism of action involves antagonism of post-synaptic dopamine D2 receptors in the mesolimbic pathway and 5-hydroxytryptamine (serotonin) 2A receptors in the frontal cortex.[3]

First approved in 1996 for treating schizophrenia, olanzapine remains a cornerstone therapy for schizophrenia, bipolar disorder, and treatment-resistant bipolar depression when combined with fluoxetine.[4,5] It also is commonly used off-label for conditions such as acute agitation, delirium, anorexia nervosa, and chemotherapy-induced vomiting.[5] Olanzapine's broad therapeutic utility stems from its dose-dependent receptor occupancy, enabling diverse clinical applications. Its rapid onset of action, particularly via intramuscular administration, which achieves peak plasma concentrations within 15-45 minutes, makes it especially effective for managing acute agitation in non-adherent or uncooperative patients.[5]

Smoking has a significant impact on olanzapine's efficacy due to the induction of hepatic Cytochrome P450 1A2 (CYP1A2) enzymes by polycyclic aromatic hydrocarbons found in cigarette smoke.[2,6] Olanzapine is primarily metabolized by CYP1A2, and its accelerated clearance in smokers often results in subtherapeutic serum concentrations, necessitating higher doses to achieve therapeutic effects.[2] Importantly, nicotine replacement therapies, such as gum or patches, and vaping do not induce CYP1A2 because they lack combustion-related hydrocarbons.[7,8] This distinction is crucial in assessing olanzapine's efficacy among smoking patients.

The prevalence of smoking in the U.S. general population was 11.5% in 2021, according to the Centers for Disease Control and Prevention.[9] However, smoking rates among individuals with mental illnesses are three to four times higher.[10,11] Given the high prevalence of smoking in this demographic, clinicians must account for patients' smoking status when evaluating olanzapine's therapeutic response.

Despite its lower risk of extrapyramidal side effects compared to first-generation antipsychotics,[12] olanzapine carries notable risks. It has a black-box warning for increased mortality in elderly patients with dementia-related psychosis.[5] Additionally, olanzapine may exacerbate metabolic issues, including hyperglycemia, dyslipidemia, and weight gain, particularly in obese patients.[13,14]

We present a case illustrating olanzapine resistance due to CYP1A2 induction by smoking, emphasizing the need for careful consideration of smoking status in treatment planning.

CASE REPORT

A 71-year-old male with a history of major neurocognitive disorder, possibly frontotemporal dementia with behavioral disturbances, alcohol use disorder, tobacco use disorder, and chronic obstructive pulmonary disease, was admitted due to worsening agitation and insomnia over the past three weeks. His home medications included aspirin 81 mg orally once daily, citalopram 20 mg orally once daily, clopidogrel 75 mg orally once daily, and zolpidem 10 mg orally at bedtime.

The patient had exhibited escalating behavioral issues, including frequent removal from local restaurants and bars for outbursts, repeated angry phone calls berating family members, and severe damage to his home. A computed tomography scan of the head without contrast on admission revealed involutional changes and atrophy with a frontal lobe predominance, as well as a prior small high-frontal infarct with encephalomalacia.

On admission, his home medications of aspirin, citalopram, and clopidogrel were continued. However, zolpidem 10 mg was discontinued to avoid potential cognitive and psychomotor side effects. A nicotine patch (21 mg/day) was initiated due to his two-pack-per-day smoking habit. The patient also was started on olanzapine at 5 mg nightly, which was titrated to 15 mg over a week to address agitation and insomnia. Despite this, his symptoms persisted, and he frequently required PRN (as-needed) medications for agitation.

The treatment team suspected a CYP1A2 interaction related to the patient's smoking, which can accelerate olanzapine metabolism, reducing its efficacy. Given the likelihood that the patient would resume smoking post-discharge, the team concluded that olanzapine might not be an optimal choice. A cross-taper from olanzapine to risperidone was initiated.

During the transition, the patient showed significant improvement. On risperidone 2 mg daily, he was noticeably calmer and no longer required PRN medications. His sleep duration also increased from an average of three hours per night to six and a half hours. The patient was eventually discharged to an assisted living facility, where he continues to do well.

DISCUSSION

Smoking has been shown to induce the activity of CYP1A2,[6] an enzyme primarily responsible for metabolizing olanzapine.[2] The processes of CYP enzyme induction and inhibition are complex and vary in their onset and resolution. Induction typically takes days to weeks, as it involves the synthesis of additional enzymes, and it may take even longer for enzyme activity to return to baseline levels after discontinuing the inducer.[15] In contrast, inhibition occurs more rapidly.

It has been demonstrated that smokers clear olanzapine more quickly, often requiring higher doses to achieve therapeutic effects.[16] In the case of our patient, even after escalating the olanzapine dose to 15 mg, symptoms failed to improve significantly. However, switching to risperidone, which is predominantly metabolized by cytochrome

P450 family 2 subfamily D member 6 (CYP2D6),[17] led to a rapid and complete resolution of symptoms.

Although it is well-established that smoking accelerates olanzapine clearance,[16] there are currently no formal guidelines for adjusting olanzapine doses based on smoking status. Research suggests that nonsmokers may require a 30-50% dose reduction compared to smokers to achieve similar plasma concentrations.[18] This poses a significant challenge for clinicians, especially since more than 60% of patients with schizophrenia are smokers.[11] Furthermore, when patients stop smoking, often during hospitalization, where smoking is prohibited, olanzapine levels can increase by 30-40% due to the loss of CYP1A2 induction, potentially leading to toxicity.[16]

Determining the appropriate olanzapine dose requires consideration of various factors, including sex, age, and the number of cigarettes smoked daily.[19] Previous reports have indicated that CYP1A2 induction reaches a ceiling effect at approximately 10 cigarettes per day, with no further induction observed beyond that threshold.[20,21] Given the elevated prevalence of smoking among patients with mental health illnesses, clinicians also must consider the duration and magnitude of a patient's smoking history when tailoring olanzapine therapy.

Awareness of CYP enzyme interactions is crucial for optimizing clinical outcomes. Selecting an alternative antipsychotic upon admission may expedite symptom resolution, reduce hospital stays, and alleviate caregiver burden. Post-discharge, the efficacy of olanzapine may diminish if patients resume smoking, further underscoring the importance of considering alternative therapies in smokers.

Additionally, increasing olanzapine doses to counteract reduced efficacy in smokers may heighten the risk of dose-related side effects, as some are metabolite-driven. A thoughtful approach to assessing smoking status and potential CYP interactions is essential for selecting the most appropriate antipsychotic regimen, ensuring therapeutic efficacy while minimizing adverse effects.[22,23]

CONCLUSIONS

Despite olanzapine's efficacy in treating various psychiatric conditions, clinicians should consider alternative antipsychotics for smokers due to its interaction with CYP1A2. This enzyme is critical to olanzapine metabolism, potentially reducing its effectiveness and requiring higher doses in smokers. Choosing antipsychotics less affected by smoking-induced enzyme activity may provide more consistent treatment outcomes and reduce the need for frequent dose adjustments. Thus, careful assessment of smoking status and its impact on drug metabolism is vital in selecting the most effective antipsychotic therapy to ensure optimal patient outcomes.

REFERENCES

[1] Zhao M, Ma J, Li M, et al. Cytochrome P450 enzymes and drug metabolism in humans. Int J Mol Sci 2021; 22(23):12808. PMID: 34884615.
[2] U.S. Food and Drug Administration. ZYPREXA Medication Guide. Lilly USA, LLC. Indianapolis, IN. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020592s074,021086s048,021253s061lbl.pdf. Accessed September 18, 2024.
[3] McCormick PN, Kapur S, Graff-Guerrero A, Raymond R, Nobrega JN, Wilson AA. The antipsychotics olanzapine, risperidone, clozapine, and haloperidol are D2-selective ex vivo but not in vitro. Neuropsychopharmacology 2010; 35(8):1826-1835. PMID: 20410873.
[4] Citrome L, McEvoy JP, Todtenkopf MS, McDonnell D, Weiden PJ. A commentary on the efficacy of olanzapine for the treatment of schizophrenia: The past, present, and future. Neuropsychiatr Dis Treat 2019; 15:2559-2569. PMID: 31564881.
[5] Callaghan JT, Bergstrom RF, Ptak LR, Beasley CM. Olanzapine. Pharmacokinetic and pharmacodynamic profile. Clin Pharmacokinet 1999; 37(3):177-193. PMID: 10511917.
[6] Dobrinas M, Cornuz J, Oneda B, Kohler Serra M, Puhl M, Eap CB. Impact of smoking, smoking cessation, and genetic polymorphisms on CYP1A2 activity and inducibility. Clin Pharmacol Ther 2011; 90(1):117-125. PMID: 21593735.
[7] Hukkanen J, Jacob P 3rd, Peng M, Dempsey D, Benowitz NL. Effect of nicotine on cytochrome P450 1A2 activity. Br J Clin Pharmacol 2011; 72(5):836-838. PMID: 21599724.
[8] Blacker CJ. Clinical issues to consider for clozapine patients who vape: A case illustration. Focus 2020; 18(1): 55-57. https://doi.org/10.1176/appi.focus.20190025.
[9] Centers for Disease Control and Prevention. Current Cigarette Smoking Among Adults in the United States. 2021. https://www.cdc.gov/tobacco/php/data-statistics/adult-data-cigarettes/?CDC_AAref_Val=https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/. Accessed September 25, 2024.
[10] Cornelius ME, Loretan CG, Wang TW, Jamal A, Homa DM. Tobacco product use among adults - United States, 2020. MMWR Morb Mortal Wkly Rep 2022; 71(11):397-405. PMID: 35298455.
[11] Sagud M, Mihaljević-Peles A, Mück-Seler D, et al. Smoking and schizophrenia. Psychiatr Danub 2009; 21(3):371-375. PMID: 19794359.
[12] Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. Am J Psychiatry 2001; 158(3):360-369. PMID: 11229973.
[13] Newcomer JW. Metabolic risk during antipsychotic treatment. Clin Ther 2004; 26(12):1936-1946. PMID: 15823759.
[14] Nicol GE, Yingling MD, Flavin KS, et al. Metabolic effects of antipsychotics on adiposity and insulin sensitivity in youths: A randomized clinical trial. JAMA Psychiatry 2018; 75(8):788-796. PMID: 29898210.
[15] Bettonte S, Berton M, Stader F, Battegay M, Marzolini C. Management of drug interactions with inducers: Onset and disappearance of induction on cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase 1A1 substrates. Eur J Drug Metab Pharmacokinet 2023; 48(4):353-362. PMID: 37278880.
[16] Lowe EJ, Ackman ML. Impact of tobacco smoking cessation on stable clozapine or olanzapine treatment. Ann Pharmacother 2010; 44(4):727-732. PMID: 20233914.
[17] Berecz R, Dorado P, De La Rubia A, Cáceres MC, Degrell I, LLerena A. The role of cytochrome P450 enzymes in the metabolism of risperidone and its clinical relevance for drug interactions. Curr Drug Targets 2004; 5(6):573-579. PMID: 15270204.
[18] Tsuda Y, Saruwatari J, Yasui-Furukori N. Meta-analysis: The effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. BMJ Open 2014; 4(3):e004216. PMID: 24595134.
[19] Horvat M, Kadija M, Ščavničar A, Živković M, Šagud M, Lovrić M. Association of smoking cigarettes, age, and sex with serum concentrations of olanzapine in patients with schizophrenia. Biochem Med (Zagreb) 2023; 33(3):030702. PMID: 37841771.
[20] Djordjevic N, Radmanovic B, Cukic J, et al. Cigarette smoking and heavy coffee consumption affecting response to olanzapine: The role of genetic polymorphism. World J Biol Psychiatry 2020; 21(1):29-52 PMID: 30513034.
[21] Moschny N, Hefner G, Grohmann R, et al. Therapeutic drug monitoring of second- and third-generation antipsychotic drugs-influence of smoking behavior and inflammation on pharmacokinetics. Pharmaceuticals (Basel) 2021; 14(6):514. PMID: 34071813.
[22] Yoshida K, Takeuchi H. Dose-dependent effects of antipsychotics on efficacy and adverse effects in schizophrenia. Behav Brain Res 2021; 402:113098. PMID: 33417992.
[23] Schoretsanitis G, Dubath C, Grosu C, et al. Olanzapine-associated dose-dependent alterations for weight and metabolic parameters in a prospective cohort. Basic Clin Pharmacol Toxicol 2022; 130(4):531-541. PMID: 35150056.

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