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Fluctuation between cigarette smoking and use of electronic nicotine delivery systems: Impact on clozapine concentrations and clinical effect

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Abstract

Unlike with smoking cigarettes, electronic nicotine delivery systems do not cause CYP450 1A2 induction as there is a lack of combustion and polycyclic aromatic hydrocarbon production. Changing to the use of an electronic nicotine delivery system from cigarettes can result in the deinduction of CYP450 1A2 and the increase of certain medication serum concentrations, including clozapine. A case is reported in which the switch from smoking to an electronic nicotine delivery system resulted in increased clozapine serum concentration and constipation, necessitating pharmacologic management. The patient ultimately transitioned back to cigarettes, which resulted in the emergence of psychiatric symptoms. An evaluation of longitudinal serum concentrations and clinical correlation is provided. It is important that patients and health care professionals have knowledge not only about the impact of smoking cigarettes on clozapine metabolism, but also the effects of switching to or from an electronic nicotine delivery system.

Keywords: smoking, cigarettes, nicotine, electronic nicotine delivery systems, CYP450 1A2, drug interaction, clozapine

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Background

Electronic nicotine delivery systems (ENDS), which deliver nicotine from a vaporized liquid, have become widely used. These devices are often referred to as "e-cigarettes" or "vape pens." As compared with smoking cigarettes, use of an ENDS does not result in combustion and, therefore, also does not result in the formation of polycyclic aromatic hydrocarbons (PAHs). The inhalation of PAHs results in increased metabolism of certain medications metabolized via CYP450 1A2.[1] Thus, it is important that health care professionals are aware of a patient's nicotine use, noting any changes in quantity or delivery mechanism. A case is reported of decreased tolerability to clozapine that correlated with an increase of the clozapine serum concentration after a patient switched from cigarette smoking to using an ENDS. This was followed by worsening psychotic symptoms when switching back to smoking.

Case Report

A 28-year-old male with no relevant medical history was prescribed clozapine 300 mg at bedtime for the manage-

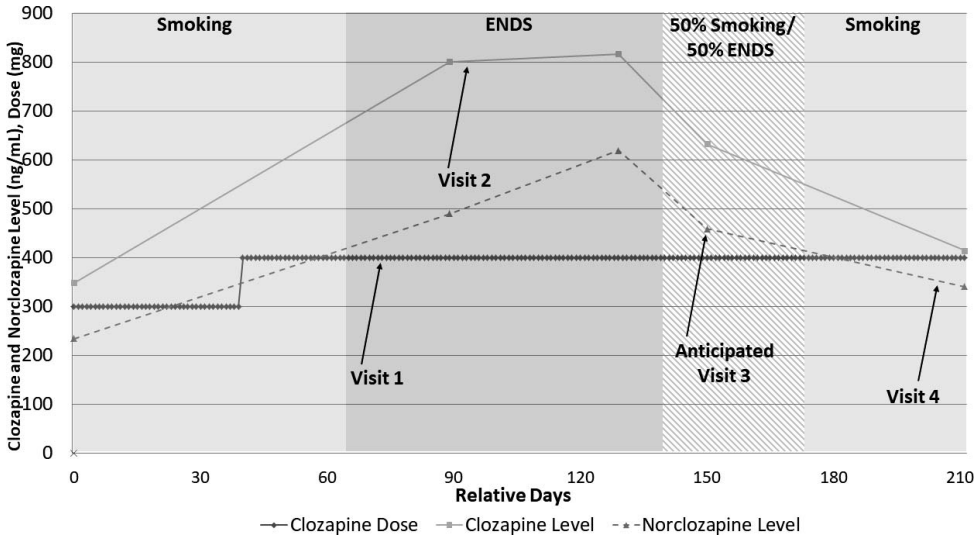

FIGURE: Serum clozapine concentrations over time (ENDS = electronic nicotine delivery system)

ment of schizophrenia. He had started clozapine approximately 5 years prior during an acute inpatient psychiatric hospitalization. He was also prescribed mirtazapine 45 mg at bedtime and extended-release venlafaxine 225 mg daily. The patient smoked 1 pack of cigarettes per day. At 300 mg and smoking, steady-state clozapine and norclozapine concentrations were 349 ng/mL and 235 ng/mL, respectively (Figure).

At an outpatient appointment with his psychiatrist (visit 1), there were no psychiatric concerns. However, the patient relayed that, 2 months prior, he had self-titrated clozapine to 400 mg at bedtime and had also switched completely from smoking cigarettes to using an ENDS. He reported having new-onset constipation and sennosides 8.6 mg-docusate 50 mg 1 tablet daily was initiated. Clozapine and norclozapine concentrations were ordered and completed just prior to the next follow-up appointment (visit 2).

At visit 2, the clozapine and norclozapine concentrations were available for review and found to be 801 ng/mL and 490 ng/mL, respectively. The change to an ENDS was believed to be the main contributing factor for the increase based on clozapine concentrations dating back 1 year (446 ng/mL) and 2 years (366 ng/mL) prior to visit 2. At those times, the patient was prescribed 400 mg at bedtime and smoking cigarettes exclusively. There was no suspicion of additional factors that might alter clozapine metabolism, such as new drug-drug interactions or an acute infectious process. There was no pharmacogenomic information available for review. During visit 2, the patient was provided psychoeducation related to clozapine and smoking along with precautions about self-adjusting medication doses. Ongoing constipation was also reported at visit 2, and sennosides 8.6 mg-docusate 50 mg was increased to 2 tablets twice daily. No other side effects manifested, and there was no change to psychiatric stability. A repeat of the clozapine and norclozapine concentrations was scheduled along with his next routine CBC approximately 4 weeks after visit 2. These repeat concentrations were similar to the previous values (clozapine: 817 ng/mL, norclozapine: 619 ng/mL). In a telephone follow-up with the patient regarding the concentrations, he voiced a desire to return to smoking cigarettes, and so the decision was made to continue clozapine 400 mg at bedtime and decrease the sennosides 8.6 mg-docusate 50 mg as needed.

Approximately 1 month after the clozapine serum concentration of 817 ng/dL was obtained, the patient did not arrive for a scheduled appointment (visit 3). The patient did, however, arrive that day to the laboratory for his monthly CBC and another clozapine concentration. The clozapine and norclozapine serum concentrations on the day of the anticipated visit 3 were 633 ng/mL and 459 ng/mL, respectively. It would later be determined the patient decreased smoking to approximately half a pack of cigarettes 2 weeks prior to the anticipated visit 3, alternating with use of an ENDS.

Two weeks later, the patient contacted his psychiatrist's office to report worsening psychotic symptoms that were significant enough to prepare for an inpatient hospitalization. However, with close monitoring by support people, hospitalization was ultimately avoided. It was near this time the patient had begun to exclusively smoke up to 1 pack of cigarettes per day and had self-initiated an old prescription of haloperidol 5 mg at bedtime due to worsening of psychotic symptoms. Collateral information from the patient's parent indicated no concern for missed doses, and it was suspected that symptoms were

exacerbated by the oscillation between cigarette smoking and use of an ENDS. Due to the COVID-19 pandemic, a virtual outpatient visit (visit 4) was scheduled. The patient scheduled this visit approximately 1 month after the time of the imminent hospitalization. The patient reported improvement in symptoms with the addition of haloperidol. The patient's constipation also resolved. Smoking cigarettes continued along with clozapine 400 mg at bedtime and haloperidol 5 mg at bedtime. The clozapine and norclozapine serum concentrations obtained a week after visit 4 were reported as 415 ng/mL and 341 ng/mL, respectively.

Discussion

Two concepts from this case are important as it relates to intermittent or variable use of an ENDS and combustible cigarettes. First, the patient had been stable on a clozapine dosage while smoking, but switching to an ENDS resulted in an increased clozapine serum concentration by more than 2-fold. Additionally, the patient developed constipation, a concentration-dependent side effect, requiring pharmacologic treatment. Although the patient did self-increase to 400 mg from 300 mg, this likely does not fully account for the degree of serum concentration elevation after review of previous years' serum concentrations and taking into account that clozapine has linear kinetics.[2,3] Second, when changing back to smoking cigarettes from using an ENDS, the patient had worsening psychotic symptoms. Although the return to smoking from an ENDS at visit 4 (with 400 mg clozapine) resulted in concentrations that were similar to those at the time of visit 1, clinically, there were important factors to consider. This includes the missed appointment, emergence of significant psychotic symptoms, and need for haloperidol. Numerous publications[4-7] note the concern of severe *rebound psychosis* with abrupt clozapine discontinuation and even dose reduction, and it is plausible that fluctuations of serum concentrations, as in this case, could produce similar effects.

At a minimum, it is important for patients to know that they are taking a medication affected by smoking, smoking cessation, or switching to another means of nicotine delivery. In psychiatry, clozapine may be the most recognized medication affected by changes in smoking patterns.[8] However, alterations in metabolism of other medications are also reported,[9] including but not limited to chlorpromazine, haloperidol, and olanzapine. Based on small pharmacokinetic studies,[10,11] even light smoking can cause increased medication clearance with 5 to 7 cigarettes being enough to maximally induce CYP450 1A2.

Despite the importance of this interaction, knowledge gaps exist surrounding the effect or lack of effect on clozapine from smoking or use of noncombustible nicotine products. A survey[12] of 184 psychiatric prescribers found only 20.4% correctly answered that chewing tobacco cessation would not affect clozapine concentrations. Unlike smoking cigarettes, which induces CYP450 1A2 through the formation of PAH, the use of ENDS, nicotine replacement therapy, chewing tobacco, and snuff does not have this effect.[13] It is also relevant to note that nonsmokers exposed to PAHs in areas with poor ventilation are at risk for increased CYP450 1A2 activity.[14,15] Deinduction occurs when a patient stops smoking or changes to a noncombustible form of nicotine. The literature[8,16] varies in descriptions of the timing of induction and deinduction with clozapine concentrations increasing significantly in as little as 4 days or as much as 2 to 4 weeks. As clozapine serum concentrations are a send-out laboratory test for many facilities and it may take several days to obtain results, any dose change should be guided by the emergence of side effects and clinical symptomatology. Different strategies to account for abrupt smoking cessation have been proposed, such as a 10% reduction every day for 4 consecutive days or a 30% to 40% reduction by 1 week.[16,17] However, these strategies may be more easily employed during an inpatient admission. In the outpatient setting, there are practical considerations, such as the complexities of frequent dose changes, the unexpected return to cigarette smoking, and as presented in this case, the switching between cigarette smoking and an ENDS. Ultimately, the prescriber should be aware of changes to a patient's pattern of cigarette smoking and use of other nicotine delivery systems.

No known cases report the effect of intermittent switching between cigarette smoking and ENDS use on clozapine concentrations. However, Kocar et al[18] describe a patient who developed side effects from increasing clozapine from 300 mg to 550 mg with an unexpected concentration of 1290 ng/mL at the latter dose. Upon investigation, it was discovered the patient had switched from smoking to an ENDS. In a second case,[19] a hospitalized patient who used an ENDS prior to admission was started on clozapine. His clozapine dose was 350 mg (serum concentration: 132 ng/mL) at the time of discharge to a chemical dependency facility. At the facility, ENDS were not permitted, and the patient began smoking approximately half a pack a day. Subsequently, the patient was reported to have worsening auditory hallucinations, paranoia, and resolution of sialorrhea. Upon discharge from the treatment program, still prescribed 350 mg, the patient switched back to using an ENDS and psychotic symptoms improved although the sialorrhea returned. Unfortunately, no serum concentrations were checked. The continued reporting of these cases is important to help bring awareness to this topic and ensure patients and health care professionals are aware of

consequences that may occur when switching between smoking cigarettes and using an ENDS.

Conclusion

Patients may alternate between smoking cigarettes and using an ENDS, which can impact clozapine metabolism. Prescribers must familiarize themselves with how these patterns of use cause either induction or deinduction of CYP450 1A2 and the resulting clinical effects. Clinical monitoring with appropriate dose adjustments is important to prevent symptom relapse or clozapine-related side effects, and obtaining serum clozapine concentrations may be useful. Proper counseling along with the routine assessment of smoking patterns or use of other methods for nicotine delivery is essential to ensure patient safety and medication effectiveness.

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