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Loxapine in patient with clozapine-resistant psychosis

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Abstract

Clozapine is recognized as the drug of choice for treatment-refractory schizophrenia, but use may be limited because of strict monitoring requirements and adverse effects including severe neutropenia, seizures, and myocarditis. Loxapine is a first-generation antipsychotic with similarities to clozapine in both structure and receptor binding. This case describes a 57-year-old male with a history of severe paranoid schizophrenia despite treatment with clozapine and other psychotropic agents, who experienced clinical improvement after a cross titration from clozapine to loxapine. Loxapine may be a reasonable alternative in patients with treatment-refractory schizophrenia who do not tolerate or respond to clozapine.

Keywords: loxapine, clozapine, schizophrenia, antipsychotic agents

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Background

Clozapine, an atypical antipsychotic, is currently the medication of choice for patients with treatment-refractory schizophrenia and is widely considered to be the most effective agent for the treatment of psychosis.[1] The US Boxed Warning associated with clozapine includes severe neutropenia (requiring routine blood monitoring, specifically absolute neutrophil count [ANC], as part of an FDA-mandated Risk Evaluation and Mitigation Strategy), seizures, orthostatic hypotension, and cardiomyopathy. Other troublesome side effects include constipation and sialorrhea.[2] Because of these risks, clozapine is often avoided by prescribers despite significant reported benefit. When patients with treatment-refractory schizophrenia are required to terminate clozapine therapy because of lack of efficacy or development of adverse effects, limited options are available. Loxapine, a dibenzoxazepine tricyclic antipsychotic, is similar to clozapine in structure and binding affinity to key receptors (Figure, Table), but with fewer drug interactions and no blood monitoring requirements.[3-5] Differences in structure and affinity include increased 5-HT2A antagonism as well as a higher affinity for dopamine-4 (D_4) receptors with loxapine.[4] Current comparative data of these 2 agents is limited, and as a result loxapine is not widely used or recognized as an alternative agent. In this case report, we discuss a patient who demonstrated a decrease in ANC and lack of clinical improvement on clozapine and valproate who was subsequently initiated on loxapine.

Case Report

A 57-year-old male with a decades-long history of paranoid schizophrenia, chronic constipation, and type 2 diabetes mellitus presented to inpatient psychiatry for months of worsening paranoia, hallucinations, disorgani-

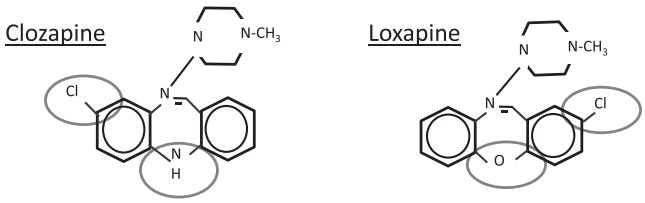

FIGURE: Chemical structures of clozapine and loxapine

zation, agitation, and verbal aggression. Prior to hospitalization, the patient lived in a group home with full-time staffing. Medications were administered to him by group home staff with no concern for medication noncompliance. The patient smoked a variable number of cigarettes, though reportedly less than a pack per day.

At the time of presentation, the patient's psychiatric medications included clozapine 700 mg daily in divided doses, lithium carbonate extended release (ER) 900 mg at bedtime, asenapine sublingual 10 mg twice daily, lorazepam 1 mg 3 times daily, and paliperidone long-acting injectable 234 mg every 4 weeks for 10 months (last administered 1 day prior to admission). Steady state clozapine and lithium levels were therapeutic at 699 ng/mL (8-hour level) and 0.86 mmol/L (12-hour level), respectively. Other medications were insulin glargine, polyethylene glycol, and simvastatin. Previous psychotropic trials included clozapine, haloperidol, olanzapine, iloperidone, quetiapine, and chlorpromazine, though doses and duration of each of these medications were unknown. Six years prior to this admission, clozapine was discontinued because of neutropenia (ANC 400/μL) while the patient was concomitantly managed with valproate. Two months prior to this admission, clozapine was added to the most recent regimen of paliperidone and asenapine for treatment-refractory symptoms. ANC at presentation was 5400/μL.

The home medication regimen was initially continued on admission while the team pursued a workup of potential medical contributors to his increased agitation. No medical concerns other than chronic constipation was identified, and the patient displayed no improvement in psychotic symptoms. On hospital day (HD) 6, asenapine was discontinued and chlorpromazine initiated because of reported benefit at doses up to 200 mg 3 times daily 2 years prior and was eventually titrated to a maximum dose of 50 mg 3 times daily. In the weeks following this change, minimal improvement in psychotic symptoms was observed, and the patient experienced worsening constipation. Valproate ER was initiated for agitation on HD 17 and titrated to 1000 mg at bedtime. The patient's steady state 25-hour total valproic acid level was low at 39.8 μg/mL on HD 21, and the dose was increased to 1250 mg at bedtime. Minimal improvement in paranoia, hallucinations, and verbal aggression resulted in the patient requiring frequent use of as needed lorazepam. Paliperidone long-acting injection due on HD 23 was not given and was instead replaced with risperidone. Chlorpromazine was also discontinued on HD 23. Oral risperidone was initiated for more flexibility of dosing at 0.5 mg at bedtime. A low dose was initiated as paliperidone was not thought to have reached steady state. Risperidone was increased to 1 mg at bedtime on HD 27. Free valproic acid levels increased with dose increase of 1000 mg to 1250 mg per day from 5.0 μg/mL on HD 24 to 7.6 μg/mL on HD 27. Levels were appropriately timed at steady state before the patient's morning doses. A total valproic acid level was not obtained during this time frame, but free levels indicated the patient was in low therapeutic range.

TABLE: Receptor binding affinities[5]

Receptor[a]	Loxapine (K_i nM)	Clozapine (K_i nM)
D2	11	160
5HT1A	2550	120
5HT2A	4.4	5.4
5HT2C	13	9.4
D1	54	270
D4	8.1	24
M1	120	6.2
Alpha 1	42	1.6
Alpha 2	150	90
H1	5	1.1

[a]H1 = histamine 1; M1 = muscarinic 1; otherwise see main text for other receptor expansions.

ANC decreased (2800/μL) on HD 27, and valproate was decreased to 1000 mg at bedtime. At this time, the team concluded the current regimen was providing more harm with the ANC decrease than benefit of clinical improvement to the patient, so alternative antipsychotic regimens were discussed, including a transition from clozapine to loxapine. On HD 29, the patient was initiated on a cross-titration from clozapine to oral loxapine over a 2-week period, with a decrease in total clozapine daily dose by 50 mg to 100 mg every other day and an increase in loxapine by 25 mg every other day. Lithium, risperidone, and valproate were continued at current doses. During this time, the team observed improvement in the patient's psychotic symptoms as well as constipation, and the daily use of as needed lorazepam decreased from 4 doses (5 mg) to 2 doses (2 mg) within 7 days. After completion of the cross-titration, the patient's ANC had normalized to 6200/μL.

In the weeks following, the patient demonstrated continued psychiatric improvement. He continued to respond to internal stimuli, but with fewer verbal

outbursts, less preoccupation with stimuli, and reduced agitation. He also showed improved communication with caregivers. The patient was discharged to a group home on HD 55 taking loxapine 100 mg twice daily, lithium 900 mg at bedtime, and valproate ER 1000 mg at bedtime.

Discussion

Clozapine is well regarded as an efficacious antipsychotic agent in patients refractory to other first-line therapies. Kane classified treatment-resistant schizophrenia as those meeting 3 criteria: (1) at least 3 trials of neuroleptic agents from 2 or more different classes in the last 5 years, at dosages equivalent to 1000 mg per day of chlorpromazine for at least 6 weeks, without symptomatic relief, (2) no period of good function in the last 5 years, and (3) a Brief Psychiatric Rating Scale score of at least 45 and a minimum Clinical Global Impression Scale rating of 4. When Kane compared clozapine to chlorpromazine and benztropine in patients meeting these criteria, clozapine demonstrated favorable responses.[6] While its exact mechanism of action in treatment-refractory psychosis is unknown, the efficacy of clozapine may be attributed to its increased affinity for serotonin receptors and decreased affinity for D2 receptors in comparison with other atypical antipsychotics.[7] However, not all patients with psychosis demonstrate adequate response to this therapy, and many discontinue the medication because of nonadherence with blood draws, severe neutropenia, or other drug-related toxicities such as seizures or myocarditis.[7] A trial of at least 8 weeks of clozapine therapy at therapeutic levels is considered adequate for clinical response.[8]

In this case, some aspects of the patient's history, including smoking habits, were unknown. Therefore, it remains a possibility that his past cigarette consumption altered his clinical response to clozapine, as cigarette smoke is a known inducer of human cytochrome P450 1A2 (CYP1A2), the primary enzyme involved in clozapine metabolism. Plowchalk and Rowland Yeo[9] confirmed increases in clearance of other CYP1A2 substrates for smokers and demonstrated increasing clearance tied to increased cigarette consumption. The patient did not have access to cigarettes nor other forms of nicotine while inpatient, which caused the team to assume smoking was not a primary contributor to lack of clozapine response.

Loxapine is an antipsychotic with similar chemical structure (Figure) and receptor binding affinities to clozapine, including a high affinity at D2 and serotonin-2A (5-HT2A; Table), but with greater 5-HT2A antagonism.[4,10] Loxapine is a potential alternative to clozapine in patients with lack of symptom improvement, difficulty maintaining adherence to blood draw requirements or adverse effects including sedation, anticholinergic effects, orthostasis, metabolic effects, or severe neutropenia.[4] Loxapine does not carry the same strict monitoring requirements as clozapine, and its side effect profile is more manageable in comparison with clozapine. Extrapyramidal symptoms are more common with loxapine, but rates of neuroleptic malignant syndrome are lower compared to clozapine and other antipsychotics.[3,7] A 2015 Cochrane review[11] suggests that loxapine has similar effects to other antipsychotics and found mixed rates of extrapyramidal adverse effects compared to atypical antipsychotics. However, studies reviewed were limited in duration of therapy, showing efficacy of loxapine in the short term of 4 to 12 weeks.[11] Despite its potential efficacy in the treatment of schizophrenia and psychosis, data on the safety and efficacy of loxapine use is limited. In this case, its favorable side effect profile in addition to theoretically comparable efficacy, loxapine was a desirable alternative to clozapine therapy.

A 1996 study[12] of 8 clozapine-resistant patients with schizophrenia evaluated adjunctive treatment with loxapine starting at 25 mg per day and increased to effect. Loxapine was associated with some clinical improvement in all patients without development of severe neutropenia or other serious adverse events, and 2 of the patients showed dramatic improvement in delusional beliefs and hallucinations such that they were able to perform independent work and education-related activities. The addition of loxapine had no effect on clozapine plasma levels, so it was concluded that the addition of loxapine did not alter the activity of clozapine but instead acted by its own mechanism. This suggests that a cross-titration from one agent to the other, as was completed in this case, is reasonable to maintain some clinical response while minimizing risk of toxicity.

A 2016 case report[13] evaluated the combination of loxapine 10 mg per day and cyproheptadine 16 mg per day therapy in the setting of a clozapine taper secondary to severe neutropenia. Researchers suggested this drug combination may mimic some of clozapine's actions because of similar binding affinities to serotonin and dopamine receptors, which allowed this change of therapy to help mitigate the risks of rapid discontinuation of clozapine therapy. No adverse effects were reported, and the patient demonstrated a decrease in delusional behavior compared with symptoms on clozapine therapy.

Conclusion

This case report highlights common challenges associated with clozapine for the treatment of psychosis and describes a successful cross-titration from clozapine to

loxapine. Loxapine may be considered as a safe alternative to clozapine for the treatment of psychosis in patients who do not demonstrate adequate response to clozapine therapy, those who experience adverse effects while on clozapine, or those who are unable to remain compliant with clozapine drug therapy and monitoring requirements.

References

1. Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtabai R, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry. 2020;177(9):868-72. DOI: 10.1176/appi.ajp.2020.177901. PubMed PMID: 32867516.
2. Mylan Pharmaceuticals Inc. Clozapine tablet; 1989 [updated 2020 Jul; cited 2020 Sep]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=883b5d43-0339-7dc1-f775-93791fb9b978
3. Mylan Pharmaceuticals Inc. Loxapine capsule; 2004 [updated 2017 Mar; cited 2020 Sep]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1a03c19b-d44f-ae98-f404-022eb8392677
4. Popovic D, Nuss P, Vieta E. Revisiting loxapine: a systematic review. Ann Gen Psychiatry. 2015;14(1):15. DOI: 10.1186/s12991-015-0053-3. PubMed PMID: 25859275; PubMed Central PMCID: PMC4391595.
5. Roth BL, Lopez E, Patel S, Kroeze WK. The multiplicity of serotonin receptors: uselessly diverse molecules or an embarrassment of riches? Neuroscientist. 2000;6(4):252-62. DOI: 10.1177/107385840000600408.
6. Kane J. Clozapine for the treatment-resistant schizophrenic. Arch Gen Psychiatry. 1988;45(9):789-96. DOI: 10.1001/archpsyc.1988.01800330013001. PubMed PMID: 3046553.
7. Solmi M, Murru A, Pacchiarotti I, Undurraga J, Veronese N, Fornaro M, et al. Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. Ther Clin Risk Manag. 2017;13:757-77. DOI: 10.2147/TCRM.S117321. PubMed PMID: 28721057; PubMed Central PMCID: PMC5499790.
8. Schulte PFJ. What is an adequate trial with clozapine?: therapeutic drug monitoring and time to response in treatment-refractory schizophrenia. Clin Pharmacokinet. 2003;42(7):607-18. DOI: 10.2165/00003088-200342070-00001. PubMed PMID: 12844323.
9. Plowchalk DR, Rowland Yeo K. Prediction of drug clearance in a smoking population: Modeling the impact of variable cigarette consumption on the induction of CYP1A2. Eur J Clin Pharmacol. 2012;68(6):951-60. DOI: 10.1007/s00228-011-1189-y. PubMed PMID: 22258279.
10. Singh AN, Barlas C, Saeedi H, Mishra R. Effect of loxapine on peripheral dopamine-like and serotonin receptors in patients with schizophrenia. J Psychiatry Neurosci. 2003;28(1):39-47. PubMed PMID: 12587849.
11. Chakrabarti A, Bagnall A, Chue P, Fenton M, Palaniswamy V, Wong W, et al. Loxapine for schizophrenia. Cochrane Database Syst Rev. 2007;4:CD001943. DOI: 10.1002/14651858.CD001943.pub2. PubMed PMID: 17943763.
12. Mowerman S, Siris S. Adjunctive loxapine in a clozapine-resistant cohort of schizophrenic patients. Ann Clin Psychiatry. 1996;8(4):193-7. DOI: 10.3109/10401239609147759. PubMed PMID: 8986313.
13. Aboueid L, McCarthy RH. Loxapine and cyproheptadine combined limit clozapine rebound psychosis and may also predict clozapine response. Case Rep Psychiatry. 2016:6123913. DOI: 10.1155/2016/6123913. PubMed PMID: 27433365; PubMed Central PMCID: PMC4940529.