Fenofibrate Induced Neutropenia During Stabilised Clozapine Therapy

Role of the Pharmacist in Identifying Adverse Reactions

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Background

Neutropenia is a widely known and severe complication of clozapine(1). This case reports severe neutropenia precipitated by the addition of fenofibrate to stabilised clozapine therapy.

Clinical Features

A 49-year-old female with a history of schizophrenia and cognitive impairment was managed with:

1. Clozapine 350 mg nocte
2. Zuclopenthixol long-acting injection 150 mg every two weeks

Initiation of fenofibrate 145 mg mane for hypertriglyceridemia precipitated asymptomatic but severe neutropenia four weeks later.

Her other medications included:

1. Escitalopram 10 mg daily
2. Rosuvastatin 10 mg daily
3. Colecalciferol 25 micrograms daily

Case Progress

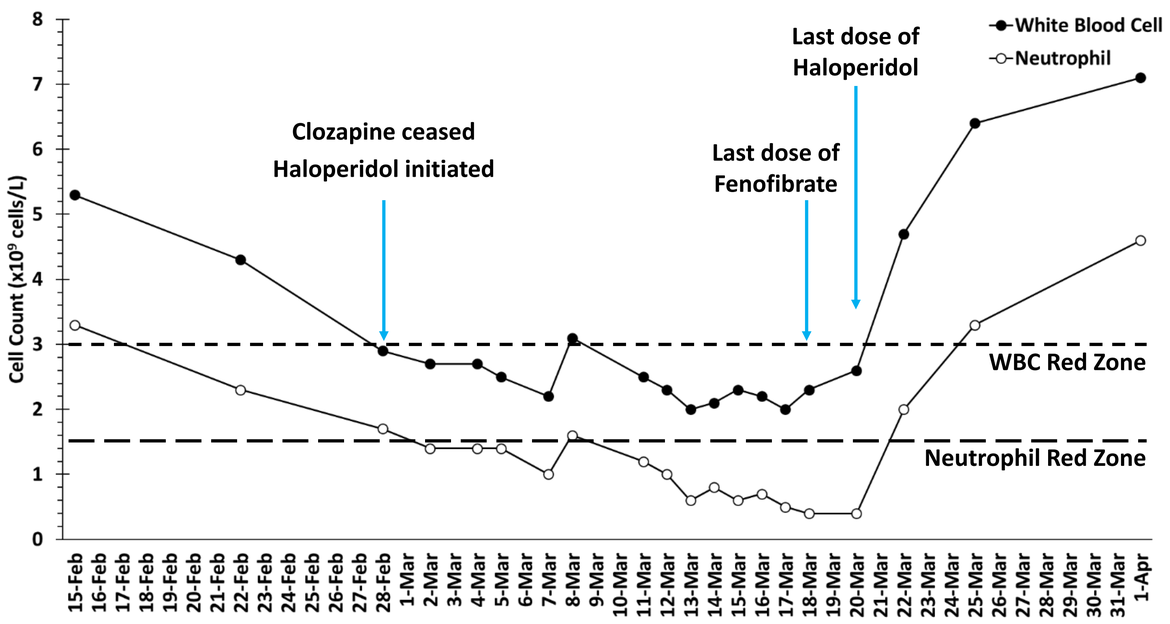

Figure 1. Changes in white blood cell and neutrophil throughout admission.

Clozapine was ceased four weeks after the initiation of fenofibrate when white blood cells decreased to 2.9 x 10^9 cells/L and neutrophils to 1.7 x 10^9 cells/L as required by the manufacturer's protocol. Haloperidol 5 mg twice daily was initiated for prophylaxis of rebound psychosis. Despite cessation of clozapine, both white blood cells and neutrophils continued to decline over the next three weeks with neutrophils reaching a nadir of 0.4 x 10^9 cells/L.

Based on the manufacturer's product information, decreases in white blood cells and agranulocytosis have been reported with the initiation of fenofibrate(2). The mechanism and frequency of adverse reactions are unknown(2).

The pharmacist performed a literature search to identify potential causes of neutropenia and identified one other case report of fenofibrate induced neutropenia. A recommendation for cessation of fenofibrate was made to the treating team. Cessation of fenofibrate resulted in a rapid normalisation of both white blood cells and neutrophils within four days with neutrophils increasing from 0.4 x 10^9 cells/L to 2.0 x 10^9 cells/L. Both clozapine and fenofibrate were not recommenced and the patient's white blood cells and neutrophils remained stable.

Discussion

Clozapine induced neutropenia and agranulocytosis generally last between one and three weeks(1). Clozapine rechallenge has been reported to result in further blood dyscrasia in 38% of patients(1). Subsequent episodes were likely to be more rapid in onset, and greater in severity and duration(1). However, 55% of patients underwent successful clozapine rechallenge and remained on treatment(1). Despite this, caution is required to not hastily attribute all neutropenia and agranulocytosis episodes to clozapine, but to consider other potential causes such as fenofibrate in this case.

Of note, other antipsychotics have also been reported to cause neutropenia and agranulocytosis(3). Furthermore, various antipsychotics may prolong the clozapine induced neutropenia episode when used for prophylaxis of rebound psychosis in place of clozapine(3). In a case series of 18 patients who experienced clozapine induced granulocytopenia, the subsequent antipsychotics used for rebound psychosis prophylaxis differed in rates of neutropenia prolongation(3):

- Quetiapine – 40%
- Olanzapine – 33.3%
- Risperidone – Nil
- Amisulpride – Nil

In this case, haloperidol was ceased two days after fenofibrate for reasons other than hematological toxicity. No studies to date have investigated whether haloperidol has a prolonging effect on clozapine induced neutropenia. However, the rapid normalization of both white blood cells and neutrophils matches the decline in plasma levels of fenofibrate rather than haloperidol (see Table 1). This suggests that haloperidol did not cause prolongation of neutropenia and the changes were likely to be independent of haloperidol.

Table 1. Pharmacokinetics of fenofibrate and haloperidol.

Drug	Half-life (h)	Note
Fenofibrate(2)	20	Half-life is for active metabolite fenofibric acid
Haloperidol(4)	20	High degree of plasma binding resulting in only 24% to 60% of drug being eliminated within one week

As fenofibrate is a likely cause of neutropenia in this case, clozapine rechallenge would likely be appropriate and successful.

Conclusion

Fenofibrate is often used to treat hypertriglyceridemia induced by clozapine therapy and clinicians should be aware that fenofibrate is a potential cause of severe neutropenia. This case highlights the role of the pharmacist to proactively identify and manage adverse drug reactions.

References

1. Bazire S. Psychotropic Drug Directory 2018: The professionals' pocket handbook an aide memoire. Stratford Upon Avon, United Kingdom: Lloyd-Reinhold Publications Ltd; 2018.
2. MIMSOnline. Lipidil: Full PI. Australia: MIMS Online; 2019.
3. Cosar B, Taner ME, Eser HY, Altinoz AE, Tarhan R. Does switching to another antipsychotic in patients with clozapine-associated granulocytopenia solve the problem? Case series of 18 patients. J Clin Psychopharmacol. 2011;31(2):169-73.
4. MIMSOnline. Serenace Tablets and Liquid: Full PI. Australia: MIMS Online; 2018.

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