

RAPID-ONSET AGRANULOCYTOSIS IN A PATIENT TREATED WITH CLOZAPINE AND LAMOTRIGINE

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SUMMARY

Background: Clozapine is the treatment of choice in drug-resistant schizophrenia. Lamotrigine is a mood stabiliser recommended as combined treatment strategy in clozapine-resistant patients. There are cases of late-onset agranulocytosis reported in literature. Some are associated with clozapine or lamotrigine, others with the combination of both.

Case report: The article presents a case of rapid-onset agranulocytosis in a 60-year old clozapine-resistant patient, in whom lamotrigine was introduced as potentiation strategy. Discontinuation of both substances and GCSF treatment resulted in normalization of the absolute neutrophil count.

Conclusions: The case suggests a possibility of developing rapid-onset agranulocytosis in clozapine-resistant patients who require lamotrigine as augmentation strategy. This emphasises the significance of monitoring a patient's blood count and early management of any dyscrasias noticed.

Key words: clozapine – lamotrigine - agranulocytosis

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INTRODUCTION

Clozapine is the treatment of choice in drug-resistant schizophrenia (Kane 1988, Mortimer 2010) with a proportion of patients responding well to clozapine monotherapy. Still, some 30% of patients exhibit clozapine-resistance despite optimised treatment and require clozapine augmentation (Buckley 2001). Lamotrigine is one of the best evidenced combined treatment strategies in clozapine-resistant schizophrenia (Dursun 1999, Zoccali 2007, Tiihonen 2009).

The key serious adverse drug reaction in clozapine treatment is agranulocytosis. Concurrently, blood dyscrasias associated with lamotrigine, such as neutropenia, leukopenia, anaemia, thrombocytopenia, pancytopenia have also been reported. It is uncertain whether potentiation strategies increase the risk of clozapine or lamotrigine-associated blood dyscrasias.

We present a case of agranulocytosis in patient receiving clozapine with rapid-onset associated with lamotrigine introduction as the augmentation strategy.

CASE REPORT

A 60-year-old woman was diagnosed with schizophrenia, paranoid type, at the age of 51. She suffered from no significant concomitant somatic disorders and presented with a history of mild hyperlipidaemia normalized with dietary intervention. There was no history of any haematologic disturbances in her and her family's medical records.

The patient was admitted to hospital due to the exacerbation of schizophrenia. She presented delusions and guttery hallucinations as well as negative symptoms

and depressed mood with marked deterioration. At first, she received olanzapine 30mg presenting no response. With the past history of non-response to two atypical antipsychotics, clozapine was introduced at 450mg a day. The absolute neutrophil count decreased slightly (to 5×10^9 cells/l) after the dose of 450mg was reached being still in a low normal range. Due to no response to clozapine after 9 weeks, lamotrigine was introduced as the augmentation strategy. The introduction of lamotrigine at a dose of 25mg resulted in a rapid decrease of the absolute neutrophil count, reaching agranulocytosis in 7 days (0.41×10^9 cells/l). Both clozapine and lamotrigine were discontinued. The neutrophil count decreased even further, reaching 0×10^9 cells/l. The patient was successfully treated with granulocyte colony-stimulating factor. After completing the GCSF therapy, a transient decrease in the absolute neutrophil count was noticed, however it normalized by itself (Figure 1).

The patient did not agree to reintroduce clozapine and was treated with quetiapine 300mg with good response and due to still present negative symptoms she was transferred to outpatient clinic. Her blood cell count is stable and still under observation.

DISCUSSION

Tourian and Margolese (2011) were the first to report a case of late-onset agranulocytosis in a patient treated with clozapine and lamotrigine at the same time. However, to our best knowledge this is the first case report to show a rapid-onset agranulocytosis that appeared during the treatment with the same combination of medicaments, at different doses in challenge-rechallenge mode.

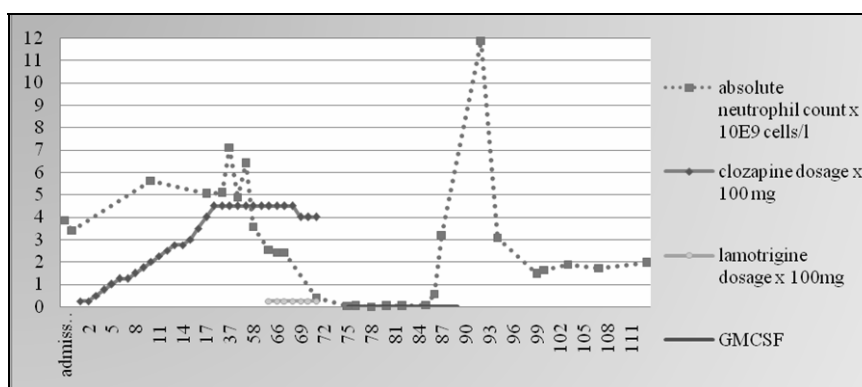


Figure 1. Average neutrophil count (x 10⁹ cells/l) with the dosages of psychotropic medications

Reports of such adverse drug reactions as agranulocytosis have been demonstrated in case of treatment with clozapine (Tamam 2001, Bhanji 2003) or lamotrigine (Das 2007, LeDrew 2005, Solvason 2000, de Camargo & Bode 1999). There are also cases of agranulocytosis seen with the combination of both drugs, when the second one is introduced after some time (Tourian 2011, Ahn 2008).

In the case described above the adverse drug reaction appeared as early as 7 days from the beginning of the combined treatment with the neutrophil count decreasing rapidly after 2 days from introduction of lamotrigine and reaching agranulocytosis (0,41 x 10⁹ cells/l) within a week. The decreasing trend was maintained for another 6 days even after discontinuing the treatment, reaching 0 x 10⁹ cells/l.

A number of factors might have contributed to the observed serious adverse drug reaction. Firstly, agranulocytosis in our patient could have been due to clozapine alone. The peak incidence of developing neutropenia or agranulocytosis falls on the first 6-18 weeks of treatment (Atkin 1996). As clozapine was introduced and continued for 9 weeks alone during the first 8 weeks we observed insignificant fluctuations of the neutrophil count and a slight decrease in the first half of week 9. Although the dose of clozapine has no impact on the risk of agranulocytosis, age and female sex, as well as dyslipidaemia and obesity are risk factors for its onset and all were present in our patient (Alvir 1993). Secondly, as the patient received lamotrigine for 7 days in low starting dosage and lamotrigine-associated agranulocytosis is reported in the literature the blood dyscrasia may result from lamotrigine treatment alone. Finally, the pharmacokinetic interaction of lamotrigine increasing the level of clozapine might have contributed to the adverse drug reaction as there is some evidence from a case report of a patient whose clozapine plasma level tripled after initiating and increasing the dose of lamotrigine (Kossen 2001).

CONCLUSIONS

The genetic hypothesis of clozapine-induced agranulocytosis reveals that patients with the HLA haplotype DQB*0502 are more likely to develop it (Dettling

2001). The studies on effects of clozapine on neutrophil kinetics proved that clozapine oxidized to a reactive nitrenium ion covalently binds to neutrophils. This increases the release of immature neutrophils from the bone marrow and shortens their half-life in the peripheral blood. The bone marrow fails to compensate for it, which may result in agranulocytosis (Iverson 2010, Ng 2014). Although the pathomechanism of agranulocytosis observed in that patient remains speculative it seems plausible it was associated with the combined effect of both drugs. As a proportion of patients with clozapine-resistant schizophrenia require augmentation strategy a risk of rapid-onset agranulocytosis with the onset of lamotrigine introduction exists. The monitoring of complete blood count at all times of clozapine treatment is crucial for the patients' safety. The paper emphasises the significance of patients' blood monitoring at the introduction of the augmentation agents and the importance of early management of drug-associated adverse reactions.

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Conflict of interest: None to declare.

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