Long-Term Treatment of Clozapine-Induced Leukopenia With Lithium: Fast-Onset Agranulocytosis Following Lithium Discontinuation

To the Editor: The atypical antipsychotic clozapine is the most effective medication for treatment-resistant schizophrenia and schizoaffective disorder, improving psychopathology and quality of life[1]; however, its use is limited by the risk of neutropenia (2.7%) and agranulocytosis (0.9%).[2] In France, after initiation of clozapine, blood monitoring must occur on a weekly basis for the first 4 months, after which patients undergo monthly monitoring.

Lithium carbonate is known to increase the white blood cell (WBC) count by a mechanism that is still unclear but that may involve demargination, stimulation of granulocyte-macrophage colony-stimulating factor, and stimulation of cytokines.[3,4] Clinicians have suggested using lithium carbonate in clozapine-induced neutropenia.[1,3]

We present here the case of a patient who benefited from clozapine rechallenge in the presence of lithium carbonate for 14 months, before lithium neurotoxicity led to a discontinuation of lithium.

Case report. Ms A is a 42-year-old maghrebian woman who was diagnosed with schizoaffective disorder (*DSM-IV-TR*) at the age of 29 years. This patient experienced mood lability and mental automatism with command hallucinations leading her to self-harm and violence against her relatives and caregivers. Her schizoaffective disorder was resistant to adequate trials of lithium, olanzapine, risperidone, amisulpride, and a combination of valproate and an antipsychotic. She was started on clozapine (to 600 mg daily). Within 2 months, hallucinations and violent behavior decreased dramatically. Twenty months after initiation of clozapine, her WBC count dropped to 2.87×10^9/L and neutrophil count fell to 1.37×10^9/L. Consequently, clozapine was stopped. The patient was then treated with a combination of valproate plus first-generation antipsychotics (haloperidol and zuclopenthixol) then valproate plus quetiapine. All were ineffective. It was decided to resume clozapine 1 year later due to increasing command hallucinations and more and more violent assaults toward patients and health professionals. A request for admission was sent to a special secure unit for dangerous patients. Her baseline WBC and neutrophil counts were in the normal range. Two months after clozapine reintroduction, the WBC and neutrophil counts fell below 3.5×10^9/L and 2×10^9/L, respectively. Lithium carbonate extended-release was then prescribed (to 800 mg daily). The WBC and neutrophil counts returned to normal range within 1 week. This combination was initially well tolerated. Improvement in psychopathology by the 2 following months enabled an end to the admission in the special secure unit, and Ms A was then hospitalized in a long-term unit specializing in socialization and rehabilitation. Fourteen months later, the patient started to experience incapacitating tremors. Although she had a plasma lithium level in the therapeutic range, tremors remained despite a decrease of the lithium dose, which was then discontinued. Two weeks later, the monthly blood monitoring showed that the WBC count had fallen to 2.35×10^9/L and the neutrophil count to 0.80×10^9/L; accordingly, clozapine was stopped. The WBC and neutrophil counts returned to normal range 2 weeks later.

The literature describing long-term use of lithium to treat clozapine-induced neutropenia is scarce. Reports of this combination have emphasized the adverse neurologic effects.[5] Our patient benefited from a long-term lithium/clozapine combination for 14 months. Unfortunately, despite the initial good tolerance, lithium had to be stopped due to neurologic impairment, and blood dyscrasia occurred within 2 weeks. Our case underlines that clinicians must carefully weigh the risks and benefits of the lithium/clozapine combination and represents a warning against discontinuing lithium once the patient is stabilized: blood monitoring must occur weekly if lithium has to be discontinued.

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Rémy Dumas, MD[a]
Rémy.DUMAS@ch-valvert.fr
Pierre Bardin, MD[a]
Christian Vedie, MD[a]

[a]Centre Hospitalier Spécialisé Valvert, Marseille, France

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