Clozapine-induced neutropenia: A review of lithium and other currently available options

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ABSTRACT

Available options are limited for patients with neutropenia needing to be initiated or maintained on clozapine therapy. A common strategy that is often utilized in these patients is the use of lithium as augmentation to clozapine, which enables the health care provider a means of continuing or initiating clozapine therapy. This article reviews the mechanism and literature evidence behind this treatment strategy.

KEYWORDS

lithium, clozapine, neutropenia

Available options are limited for patients with neutropenia needing to be initiated or maintained on clozapine therapy. A common strategy that is often utilized in these patients is the use of lithium as augmentation to clozapine, which enables the health care provider a means of continuing or initiating clozapine therapy. Clozapine is the most effective antipsychotic based on data from the U.S. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[1] and the UK Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS),[2] but comes with the associated risk of neutropenia. This article reviews unique aspects of using lithium as an augmentation to clozapine, as well as other strategies that can be considered for maintaining or initiating clozapine therapy in patients with neutropenia.

Many times our biggest challenge in using clozapine is finding a way to keep patients from developing neutropenia and keeping the absolute neutrophil counts (ANC) ≥1500mm^3 and white blood cell (WBC) counts ≥3000/mm.^{3} This is not an uncommon problem that health care providers encounter with patients on clozapine therapy. The conveyed frequency of agranulocytosis (<100 cells/mm^3) and granulocytopenia (< 1500 cells/μL) is 0.6% and 28%, respectively.[3] The Clozaril Patient Monitoring Services revealed 0.4% of patients had pre-treatment white blood cell counts too low to allow initiation of clozapine. Of these patients, 75% were of African or African-Caribbean descent,[4] likely due to the increased leukocyte marginalization that has been shown to be more prominent in these populations. Of all neutrophils in the body, 90% reside in the bone marrow and the remainder circulates freely in the blood or deposits next to vessel walls (marginalization). The addition of lithium has been shown to increase neutrophil counts by 2000/mm,[3] which is in part through demarginalization of leukocytes.[5] This increase is not dose related but may require a lithium level of 0.4-1.1 mEq/L depending upon each individual patient.[6] Since leukocyte marginalization appears to be more consistent in patients of African or African-Caribbean descent, it stands to reason that demarginalization of leukocytes caused by lithium may have more prominent effects in these populations.

A commonly asked question regarding lithium-induced leukocytosis is if this desired side effect increases the body's ability to fight off infection. To answer this question, we need to understand how lithium is proposed to cause leukocytosis. Lithium not only works by demarginalization or redistribution of granulocytes in the marrow reserve, but also by upregulation of granulopoiesis-stimulating factors, in addition to hypercortisolaemia.[6] Hematological parameters

gradually improve during the first week of lithium administration, consistent with the time frame of patients administered granulocyte–macrophage CSF (GMCSF) or granulocyte colony-stimulating factors (G-CSF),[3] which are known to boost the immune system to aid in fighting off infections. Lithium opposes prostaglandin E2, which has been demonstrated to have effects on bacteria, parasites, and even pathogenic fungi.[7] Prodigious production of prostaglandin E2 causes stimulation of microorganisms and suppression of humoral and cell-mediated immunity.[7] Immunostimulation is nonspecific and may be relevant to different types of infections. Lithium has been shown to inhibit the replication of type 1 and 2 herpes virus in cell cultures, in addition to reportedly inducing remission of viral infections such as sinusitis, sinobronchitis, frequent colds, sore throats, cold sores and genital herpes.[8-13] A 29-year-old woman with a long history of recurrent skin infections was shown to have diminished polymorphonuclear neutrophil cAMP levels and restored normal chemotactic responsiveness when administered lithium and relapsed when lithium was discontinued.[7] In contrast, other articles have shown lithium-induced neutrophils in vitro showing less bactericidal properties then non-lithium induced neutrophils.[14]

Another strategy for obtaining appropriate WBC and ANC levels that will enable clozapine initiation and/or continuation would be to obtain blood samples later in the day. A recently published study compared the same set of patients having early morning blood draws to blood draws taken later in the day (mean sampling time - pre/post was 5 hours 24 minutes).[15] A difference in pre/post time change in WBC values were shown to be marginally significant (mean increase=667/mm3, p=.07), with a significant difference (mean increase=1,130/mm^3, p=.003) between the pre/post time change in ANC values. ANC values were impacted to a greater extent by the time change than WBC values in this sample.

A strategy implemented at our facility exploiting this diurnal variation in neutrophil function, which assists in initiating and continuing clozapine therapy, is utilizing a point-of-care (POC) lab device, which can be purchased for around $14,000. This device allows a complete blood count (CBC) plus 3-part differential to be completed by finger stick requiring 5-6 drops of blood instead of weekly blood draws that both patients and health care providers find to be a major barrier to clozapine therapy. Many factors, including patient irritation and violent behavior when having their blood drawn on a consistent basis, have been noted by our physicians as the biggest obstacle in utilizing clozapine. Another obstacle is contracting out with a clinical laboratory, which typically means patients will receive early morning blood draws. A point-of -care lab device not only allows labs to be drawn at a later time of the day, but also allow patients a less invasive means to acquire lab draws on a consistent basis.

Changing the time at which blood draws are taken during the day may allow for clozapine continuation by limiting the risk of pseudoneutropenia; however it remains the clinician's responsibility to discern between benign or malignant neutropenia.[15] It is recommended that patients with WBC values trending down or below the predefined criteria have labs redrawn several hours after the morning lab, prior to discontinuing clozapine therapy.[15] If the addition of lithium is used as augmentation to clozapine therapy for the prevention or correction of neutropenia, it still remains a matter of clinical judgment and should be based upon each individual patient. According to the available literature, lithium appears to not only help prevent patients from developing neutropenia, but is also a relatively safe medication if monitored appropriately.

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