Clozapine-Induced Procalcitonin Elevation

To the Editor: Clozapine is the only antipsychotic approved for treatment-resistant schizophrenia.[1] Despite this approval, its use is limited due to potentially life-threatening side effects.[2] Serious (such as neutropenic sepsis) and milder (such as clozapine-induced fever[3] and flu-like symptoms[4]) conditions make the differential diagnosis of fever in clozapine treatment a clinical challenge.[5] Fever and C-reactive protein (CRP) elevation with or without myocarditis[7] have also been described.[6] We report the case of a patient who experienced fever with CRP and procalcitonin (PCT) elevation while taking clozapine. PCT is the best diagnostic predictor of bacterial infection in febrile patients.[8,9] However, after a comprehensive evaluation, no evidence of infection[3] was found. We postulate that clozapine induced an increase in both PCT and CRP levels, challenging the usefulness of these biomarkers in this clinical context. To our knowledge, the association between clozapine-induced fever and PCT elevation has not yet been reported in the literature.

Case report. Mr A is a 46-year-old man diagnosed with schizophrenia (*ICD-10* criteria) at the age of 20 years. He had received no psychiatric follow-up or psychopharmacologic treatment since age 22 years. The patient was admitted to the psychiatric ward on July 2016 after a suicide attempt by defenestration secondary to command hallucinations. During the psychopathological evaluation, auditory, visual, and somatic hallucinations; thought broadcasting; and persecutory and mystic delusions were also identified. His Positive and Negative Syndrome Scale (PANSS)[10] score was 131.

At admission, paliperidone was initiated up to 12 mg/d. Mr A remained symptomatic, thus he was switched to haloperidol 9 mg/d during the following weeks, and zotepine 100 mg/d was subsequently added in combination. Because of the persistence of psychotic symptoms, those antipsychotics were stopped. He was switched to clozapine, initiated on a conservative titration schedule and increased to 250 mg/d, with normal complete blood cell (CBC) count results.

On day 10 of clozapine treatment, Mr A developed pyrexia (101.48° F, tympanic) with CRP elevation (1.63 mg/dL, upper limit of normal: 0.5 mg/dL); he had no other symptoms and normal physical examination results. On the twelfth day, his CBC was within normal limits, except for lymphopenia (0.93×10^9/L), and his troponin and creatine kinase values were within the normal range. The echocardiographic evaluation showed mild left ventricular dilatation, hypokinesia, and systolic dysfunction. For 4 days, intermittent pyrexia was observed (up to 103.46° F, tympanic), with effective fever control with acetaminophen. Chest x-ray and blood and urine cultures were performed, but no focus of infection was identified.[11] On the fourteenth day, his CRP levels remained high (29.54 mg/dL); PCT was quantified and levels were elevated (12.2 ng/mL, upper limit of normal: 0.5 ng/mL). Given these findings and the temporal association with clozapine, no antibiotic was initiated,[4] and clozapine was switched to olanzapine. In less than 24 hours, his PCT and CRP levels decreased; the patient became apyretic within 48 hours. Inflammatory markers completely normalized in 7 days. Psychotic symptoms improved (PANSS score = 82) after 2 weeks, and he was referred to a psychiatric day hospital. No clinical or laboratory changes have been observed since that time. The adverse effect of clozapine was reported to the national pharmacovigilance system.

This is the first reported case of clozapine-induced PCT elevation. PCT (specificity of 81%) is superior to CRP (specificity of 67%) as an indicator for differentiating bacterial from noninfective causes of inflammation.[12] Although Mr A had high levels of PCT and CRP, he showed no focus of infection. Ronaldson et al[13] have shown that with clozapine-induced myocarditis, CRP levels rise with the onset of fever, and raised troponin level or left ventricular impairment emerges after 3–5 days. Taking these findings into consideration, we cannot exclude the possibility that Mr A developed subclinical myocarditis.

Whatever the definitive diagnosis, the usefulness of PCT in clozapine-induced fever might be considered unclear, as PCT levels can rise in the absence of bacterial infection. Given our findings, it is important that both PCT and CRP levels be interpreted together with all clinical and laboratory information.

References

1. Warnez S, Alessi-Severini S. Clozapine: a review of clinical practice guidelines and prescribing trends. *BMC Psychiatry*. 2014;14(1):102.
2. Lee J, Takeuchi H, Fervaha G, et al. The effect of clozapine on hematological indices: a 1-year follow-up study. *J Clin Psychopharmacol*. 2015;35(5):510–516.
3. Štuhec M. Clozapine-induced elevated C-reactive protein and fever mimic infection. *Gen Hosp Psychiatry*. 2013;35(6):680.e5–680.e6.
4. Pui-yin Chung J, Shiu-yin Chong C, Chung KF, et al. The incidence and characteristics of clozapine-induced fever in a local psychiatric unit in Hong Kong. *Can J Psychiatry*. 2008;53(12):857–862.
5. Manu P, Sarpal D, Muir O, et al. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? a systematic review of the published literature. *Schizophr Res*. 2012;134(2–3):180–186.
6. Löffler S, Löffler-Ensgraber M, Fehsel K, et al. Clozapine therapy raises serum concentrations of high sensitive C-reactive protein in schizophrenic patients. *Int Clin Psychopharmacol*. 2010;25(2):101–106.
7. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust N Z J Psychiatry*. 2011;45(6):458–465.
8. Shi Y, Peng JM, Hu XY, et al. The utility of initial procalcitonin and procalcitonin clearance for prediction of bacterial infection and outcome in critically ill patients with autoimmune diseases: a prospective observational study. *BMC Anesthesiol*. 2015;15:137.
9. ten Oever J, Netea MG, Kullberg BJ. Utility of immune response-derived biomarkers in the differential diagnosis of inflammatory disorders. *J Infect*. 2016;72(1):1–18.
10. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
11. Lowe CM, Grube RRA, Scates AC. Characterization and clinical management of clozapine-induced fever. *Ann Pharmacother*. 2007;41(10):1700–1704.
12. Simon L, Gauvin F, Amre DK, et al. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis*. 2004;39(2):206–217.
13. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Evolution of troponin, C-reactive protein and eosinophil count with the onset of clozapine-induced myocarditis. *Aust N Z J Psychiatry*. 2015;49(5):486–487.

Tiago A. Duarte, MD[a]
tantunesduarte@gmail.com
Filipe D. G. Godinho, MD[a,b]
André L. B. Ferreira, MD[a]
Frederico Simões do Couto, MD, PhD[a,c]
Paulo T. Martins, MD[a,c]

[a]Serviço de Psiquiatria e Saúde Mental, Hospital de Santa Maria—Centro Hospitalar Lisboa Norte, Lisboa, Portugal
[b]Departamento de Psiquiatria e Saúde Mental, Hospital do Espírito Santo de Évora, EPE, Évora, Portugal
[c]Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal

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