Should we routinely add CRP to clozapine titrations? – Learning from three cases

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Objectives: An international guideline recently provided certain personalized schedules for titrating clozapine in adult inpatients by considering: 1) DNA ancestry group, 2) sex-smoking subgroup, and 3) presence/absence of clozapine poor metabolizer (PM) status. Measuring CRP levels at baseline and during the first 4 weeks is recommended. Titrations too fast for the metabolism of specific patients can lead to clozapine-induced inflammations and CRP elevations. **Methods:** Three published cases are reinterpreted. Better outcomes might have been obtained by using the guideline. **Results:** Case 1 was a Chinese male non-smoker, a clozapine PM due to an underlying inflammation. Case 2 was a Turkish female non-smoker who developed clozapine-induced myocarditis in the context of 4 risk factors (undiagnosed inflammation, obesity, valproate and olanzapine co-prescription). Case 3 was a United States patient of European ancestry with no known risk factors who developed myocarditis after a routine titration and had an unsuccessful rechallenge with 12.5 mg/day. Application of the international clozapine titration guideline may have prevented: 1) Case 1 by recommending against clozapine titration for a patient with an abnormal CRP level, 2) Case 2 by considering 4 risk factors and using a slow titration for clozapine PMs, and 3) Case 3 by using CRP elevations for early identification of a possible genetic PM. **Conclusions:** When baseline or prior CRPs are normal and then become abnormal during a clozapine titration, this indicates: 1) clozapine-induced inflammation associated with too-rapid titration for that specific patient, and/or 2) co-occurrence of an infection. Prospective studies need to verify this hypothesis.

(Neuropsychopharmacol Hung 2022; 24(4): 153–161)

Keywords: clozapine/adverse effects, clozapine/blood, clozapine/metabolism, CYP1A2, inflammation, myocarditis/chemically induced, myocarditis/etiology

INTRODUCTION

This article describes information on clozapine that is not provided in the United States (US) package inserts approved by the Food and Drug Administration (FDA) or in US textbooks. The reader may be skeptical of this type of information, which may contradict what he/she has been taught on clozapine (de Leon, 2023). A comprehensive discussion of the clozapine story requires presenting a more complex picture. What we know and do not know of clozapine can be better understood when we compare clozapine history with the haloperidol story and the risperidone story.

Chlorpromazine was introduced in France in 1952 by Delay and Deniker and reached the US in 1954. Clozapine was synthesized in 1958, in the era of the first-generation antipsychotics. Several clinicians tried to use it in their patients but were unsuccessful due to adverse drug reactions (ADRs). A group of German-speaking psychiatrists led by Hippius led to clozapine's marketing in Central Europe in the 1960s; they kept it alive in the 1980s after the agranulocytosis scare until clozapine was approved in the US in 1989 (de Leon et al., 2022a).

Haloperidol was marketed in Europe in the 1950s and in the US in 1961. At that time no randomized clinical trials (RCTs), pharmacokinetic studies or large studies of ADRs were required. The FDA never required RCTs for haloperidol as it was already approved and there was no funding mechanism to conduct RCTs once haloperidol became generic. Additionally, there was no requirement to update the haloperidol package insert based upon advanced knowledge gained from subsequent study by independent investigators. Thus, the US package insert and US textbooks do not explain that glucuronidation is the most important metabolic pathway for haloperidol or that consideration of inhibitors or inducers is required for personalizing haloperidol dosing (McGrane et al., 2022). Even though haloperidol was approved at a time when large doses of FGAs were the norm, its package insert has never been modified. Therefore, US clinicians may not be sufficiently aware that in high doses haloperidol still causes lethality in the US due to Torsades de Pointes. This is particularly true for high parenteral doses of haloperidol (Wahidi et al., 2016). As haloperidol lethality from ADRs is not well understood by prescribers, clozapine lethality from ADRs is also not well understood by prescribers. Based on the US package insert and US textbooks, US clozapine prescribers are aware that clozapine can cause agranulocytosis but are not sufficiently aware of the lethality of other ADRs in clozapine patients. This may also be challenging for worldwide prescribers (de Leon, 2023). From 2000 to 2019, prescribers around the world reported 29,586 cases of potential agranulocytosis to the ADR database of the World Health Organization. These cases led to 433 deaths with a relative lethality of 1% (de Leon et al., 2022b). Some of the prescribers in the US and around the world may not know that two other ADRs caused more deaths in clozapine patients than agranulocytosis. In this period, there were 1922 deaths due to pneumonia (30% relative lethality; 1922/6506) and 484 deaths due to myocarditis (11% relative lethality; 484/4536) (de Leon et al., 2022b).

Risperidone was marketed in the US in 1993; at that time RCTs and large studies of ADRs were required but pharmacokinetic studies and personalized dosing were not required. As a matter of fact, risperidone was approved for schizophrenia up to 16 mg/day, an extremely high dose by current standards. Current risperidone dosages in schizophrenia are typically not more than 6 mg/day, but US prescribers may not be aware that risperidone poor metabolizers (PMs) may require only half of that dosage due to 1) genetic deficiency in the CYP2D6 gene, 2) co-prescription of CYP2D6 inhibitors or 3) renal impairment. As with risperidone, clozapine prescription also suffers from lack of sufficient understanding by prescribers on the need for personalized dosing (de Leon, 2022a).

UPDATING CLOZAPINE KNOWLEDGE OF PERSONALIZED DOSING

Clozapine is mainly metabolized by the cytochrome P450 1A2 (CYP1A2) which follows 3 major levels of activity based on ancestry: 1) lowest in Asians and their descendants, the original inhabitants of the Americas, people described in the US using the terms Native American or Hispanic (although some of the Hispanics may have European or mixed ancestry); 2) intermediate in Europeans, usually called Caucasians in the US; and 3) highest in individuals of African descent (de Leon et al., 2022c). Within each of these 3 ancestry groups, female non-smokers have the lowest ability to metabolize clozapine while male smokers have the highest. Some individuals, called CYP1A2 PMs, behave as though they have little CYP1A2 activity and need approximately half the usual clozapine dosage. Clozapine PM status can be explained by rare genetic mutations, inflammation, obesity or inhibitors including oral contraceptives,

valproic acid (VPA) or high intake of caffeine (Ruan and de Leon, 2020).

When clozapine is titrated too fast for a specific patient's metabolism, he or she can develop clozapine-induced inflammation that manifests as elevations in c-reactive protein (CRP). The cytokines released by the inflammation inhibit CYP1A2 and cause positive feedback; when the titration is continued, auto-immune response can lead to myocarditis (Ertuğrul et al., 2021; Koenig et al., 2022) or other types of clozapine-induced manifestations. Verdoux et al. (2019) proposed that manifestations of clozapine-induced inflammation due to rapid titration may include a wide variety of presentations including: 1) systemic inflammatory processes: fever, fever with isolated CRP elevation, OR lupus; or 2) localized signs of inflammation: myocarditis, serositis, pneumonitis/alveolitis, hepatitis, pancreatitis, nephritis, colitis and dermatological disorders. This classification is somewhat arbitrary since these presentations may lie on a continuum with no clear-cut boundary between them, and several conditions may co-occur (de Leon, 2022c).

In order to prevent titrations that are too rapid, an international guideline was recently published that provides 6 personalized schedules for titrating clozapine in adult inpatients (de Leon et al., 2022c). The 6 titrations are personalized according to the dosages needed for reaching trough steady-state plasma concentrations > 350 ng/ml, which is considered the minimum therapeutic concentration. The 6 different titration schedules consider 3 parameters: 1) DNA ancestry group, 2) sex-smoking subgroup, and 3) presence or absence of clozapine PM status.

The titration guideline recommends measuring CRP levels with the weekly absolute neutrophil count (ANC) at baseline and during the first 4 weeks of titration (de Leon et al., 2022c). A titration that is too fast for the clozapine metabolism of that specific patient can cause a clozapine-induced inflammation and CRP elevations. Rapid titrations can also lead to aspiration pneumonia (Schoretsanitis et al., 2021).

METHODS

In a recent survey of US psychiatrists, only 18% used a myocarditis screening protocol (Cotes et al., 2022). Most of the readers may have never seen a recommendation for CRP monitoring during clozapine titration. Aided by CRP monitoring and using an approach considering clozapine's pharmacokinetics, the fourth author concluded that one of his patients who developed clozapine-induced myocarditis (Cook et al., 2015) actually was a clozapine PM due to obesity and co-prescription of VPA (Koenig et al., 2022). Because the fourth author is convinced that the pharmacokinetic reinterpretation of that case is correct, this article further extends this framework in providing a reinterpretation of 3 prior published cases from 3 different countries, China (Ruan et al., 2019; 2020), Turkey (Anıl Yağcıoğlu et al., 2019; Ertuğrul et al., 2021) and the US (Koenig et al., 2022). Table 1 presents a brief version of the clinical data of the three patients. Next, we provide a reinterpretation of the cases to highlight the wisdom of CRP monitoring. We propose that if these patients had been titrated using the recently published international guideline and CRP measures, their clozapine titration would not have led to ADRs and their cases would not have been published.

RESULTS

Preventing clozapine-induced inflammation in Case 1

Case 1 was a Chinese male non-smoker whom we first wrongly identified as a possible genetic PM (Ruan et al., 2019). During the writing of a second article focused on infections in this clozapine cohort, we realized that this patient had an underlying inflammation that was undiagnosed by the treating psychiatrist (Ruan et al, 2020). The underlying undiagnosed inflammation led the patient to behave as a clozapine PM. Chinese male non-smokers usually need around 210 mg/day of clozapine to reach 350 ng/ml, but according to his plasma concentration this patient only needed 90 mg/day to reach 350 ng/ml. The prescriber uptitrated the patient to 175 mg/day on day 8. Moreover, the initial dose of 50 mg/day was extremely high for a clozapine PM with an underlying inflammation; it led to the addition of a clozapine-induced inflammation (due to titration that was too rapid for the metabolism of this patient). The treating clinician was fortunate to have easy access to plasma clozapine concentrations so, after seeing 3 high values, the clozapine dose was decreased from 150 mg/day to 75 mg/day, leading to improved CRP values. The patient was discharged on 125 mg/day on day 76 with an undiagnosed underlying inflammation. The guideline would have recommended not starting clozapine until the underlying inflammation had been diagnosed and corrected.

Table 1. Description of 3 patients whose titrations might have benefited from using the new guideline with personalized titrations

	Clozapine D for 350 ng/ml	D during titration Guideline vs. used				Outcome
Age (yr) sex smoking	Expected vs C	1st	7-day	14-day	21-day	
Case 1: Chinese PM (undiagnosed inflammation): access to serial clozapine levels led to a dramatic ↓ D						
31-yo ♂ non-smoker	210 vs. 90[a]	12.5 vs. 50	50 vs. 125	100 vs. 175	150 vs. 150	Day 2, D=50 led to tachycardia
↑ CRP since day -36[b]						
↑ CRP on day 13						Days 13 and 20 very high clozapine C
↑↑ CRP on day 21[b]						On day 28 D was decreased to 75
						On day 76 discharged on D=125 with an undiagnosed inflammation
Case 2:[c] Turkish PM (undiagnosed infection, obesity, OLA and VPA) with myocarditis due to a rapid titration in week 3 (after day 14)						
19-yo ♀ non-smoker	236 vs. 130[c]	12.5 vs. 12.5	50 vs. 50	75 vs. 200		
↑ CRP on day 1[d]						Day 15 diagnosis of urinary tract infection.
↑ CRP on days 14, 17 & 19						Day 19 supraventricular tachycardia, ↑ troponin, and pericardial effusion in echo.
						Day 20 clozapine was stopped.
Case 3:[e] Genetic PM (European ancestry) who had myocarditis with a normal US titration and could tolerate rechallenge.						
31-yo ♂ non-smoker	119 vs. 457[e]	25 vs. 25	100 vs. 100	150 vs. 150		Day 7 psychosis improved (D=100)
↑ CRP on day 15						Day 15 tachycardia, chest pain and ↑ troponin
						Day 16 diagnosis of myocarditis; clozapine d/c
						Patient had severe agitation and psychosis with repeated skin abscess at injection sites
Normal CRP on day 148		12.5 vs. 12.5[f]	50 vs. 12.5[f]	Stopped		Day 149 D=12.5 is started
↑ CRP on days 155, 158 & 161						Day 151 macopapular rash
						Day 161 (day 13 of 2nd titration) clozapine D/C
						Day 162 acute pericarditis was diagnosed
						Day 165 recovered but eosinophilia persisted

C: concentration; CRP: c-reactive protein; D: dose; D/C: discontinued; DRESS: drug reaction with eosinophilia and systemic symptoms; OLA: olanzapine; PM: poor metabolizer; US: United States; VPA: valproate.

[a] The patient appears to be a clozapine PM based on the mean of 7 Cs during titration; we estimated he only needed 90 mg/day to reach 350 ng/ml, which is clearly lower than the 210 mg/day which is the mean D for average Asian ♂ non-smokers. These 7 Cs were contaminated by the underlying inflammation.

[b] The treating psychiatrists did not pay sufficient attention to know that before starting clozapine the patient had an undiagnosed inflammation. On day 21 the rapid titration led to a clozapine-induced inflammation, so his CRP was double the baseline value and reflected the underlying undiagnosed inflammatory process plus the added clozapine-induced inflammation.

[c] The patient appears to be a clozapine PM based on a C during titration; we estimated she only needed 130 mg/day to reach 350 ng/ml, which is clearly lower than the 236 mg/day which is the mean D for average European ♀ non-smokers. The only C was contaminated by the underlying inflammation. The PM status was a combination of the inflammation, obesity, VPA and olanzapine.

[d] As the patient was asymptomatic, the abnormal CRP on day 1 received no attention. In retrospect, we think that the patient probably had a urinary tract infection before starting clozapine.

[e] The patient appears to be a clozapine PM based on a C during titration; we estimated he only needed 119 mg/day to reach 350 ng/ml, which is clearly lower than the 457 mg/day which is the mean D for average US ♂ non-smokers. The 1 concentration was contaminated by the underlying inflammation. There was no obvious reason for PM status, so we assumed that he was a genetic PM. Two alleles (CYP1A2*6 and CYP1A2*7) have been associated with low CYP1A2 activity in people of European ancestry. They cannot be tested by commercial laboratories.

[f] Once it was clear that the patient was a genetic PM, the titration guideline would have recommended the lowest D possible in the US, 12.5 mg/day. The patient could not tolerate that D and developed DRESS. That D was stopped on day 13 of the second titration. It is very possible that the patient had developed auto-antibodies with the first titration which were still present 3 months later, so he had an extremely fast and pronounced response during the second titration.

Preventing inflammation in a patient with multiple risks: Case 2

Case 2 was a Turkish female non-smoker who developed clozapine-induced myocarditis (Anıl Yağcıoğlu et al., 2019). A reinterpretation of the case (Ertuğrul et al., 2021) led to finding 4 risk factors identified in the clozapine titration guideline: an undiagnosed inflammation (possibly from a urinary tract infection), obesity plus VPA and olanzapine co-prescriptions.

No baseline CRP was available but CRP was abnormal on day 1, indicating that before clozapine some inflammatory process was present. She was diagnosed with a urinary tract infection on day 15, so we suspect that this infection was present before clozapine was started. The treating psychiatrist was not aware that obesity and VPA made the patient a clozapine PM. Turkish female non-smokers are similar to European female non-smokers and usually need around 236 mg/day of clozapine to reach 350 ng/ml. According to her plasma concentration the patient only needed 130 mg/day to reach 350 ng/ml but the prescriber uptitrated to 250 mg/day. The titration was started with 12.5 mg/day, which is appropriate for this patient, but on day 14 the dose was increased to 175 mg/day which is much higher than 100 mg/day recommended by the guideline for clozapine PMs of European ancestry. On day 19, the first signs of myocarditis were evident and clozapine was stopped on day 20.

First, the guideline would have recommended not starting clozapine until the cause of abnormal CRP was identified. Second, the titration in the third week (after day 14) would have been much less pronounced, possibly preventing myocarditis.

The most recent update on the guideline has recommended that when patients are started on clozapine while taking olanzapine or quetiapine, they should be placed in the titrations for clozapine PMs for that ancestry group (Schoretsanitis and de Leon, 2022). Adding clozapine to olanzapine appears to increase the seriousness and lethality of clozapine-induced myocarditis during titration (De Las Cuevas et al., 2022a). During clozapine-induced myocarditis, clozapine metabolism is probably saturated and olanzapine is mainly metabolized by CYP1A2, so in this circumstance olanzapine can behave as a competitive inhibitor and further decrease metabolism (Schoretsanitis and de Leon, 2022).

In summary after a retrospective interpretation compiled after many years of increasing our knowledge, we realized this patient had 4 risk factors for clozapine-induced myocarditis (underlying inflammation, obesity, VPA and olanzapine co-prescriptions) which reduced her ability to metabolize clozapine. Moreover, it was not a good idea to reach a clozapine dose of 200 mg/day on day 14 in this patient.

Preventing inflammation in a genetic clozapine PM: Case 3

Case 3 was a US patient of European ancestry (or Caucasian) who was most perplexing. He developed myocarditis after a routine titration in a US hospital with awareness that rapid titration can contribute to clozapine myocarditis. This patient was treated in 2019, after 3 prior cases of myocarditis had been associated with rapid titrations in the context of VPA co-prescription (Chopra and de Leon, 2016; Koenig et al., 2022). The patient had no known risk factor for myocarditis and started to show improvement on day 7 with a clozapine dose of 100 mg/day. On day 14, a dose of 150 mg/day was prescribed and on the next day CRP was abnormal and other signs of myocarditis appeared. US male non-smokers may need around 457 mg/day of clozapine to reach 350 ng/ml. According to his plasma concentration the patient only needed 119 mg/day to reach 350 ng/ml but the prescriber increased dosage to 200 mg/day. It was extremely unfortunate that a rechallenge several months after the first clozapine trial was not successful. The patient could not tolerate 12.5 mg/day, which led a complex immunological reaction with a skin rash, CRP elevation, eosinophilia and pericarditis. The first time, clozapine-induced myocarditis was diagnosed but the second time, it appeared more compatible with clozapine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) (de Filippis et al., 2022).

During the first clozapine trial, he developed myocarditis, which was possibly explained by auto-antibodies or another auto-immune mechanism. The auto-antibodies (or auto-immune phenomena) were still present 3 months later and led to a very fast auto-immune response manifested with DRESS syndrome after a very small clozapine dose.

As clozapine PM status was not explained by obesity, any known inflammation or co-medication, as far as we can tell the patient probably was a genetic clozapine PM. Genetic clozapine PMs may need extremely low daily doses of clozapine (75-150 mg/day in Asians and possibly 75-200 mg/day in Europeans) to reach the

minimum therapeutic clozapine concentrations of 350 ng/ml. Thus, even the slow titrations recommended in the clozapine guideline may be too fast for clozapine PMs.

It is possible that in the future, after extensive research, clozapine PMs will be identified by CYP1A2 genotyping before starting clozapine. At this time, our knowledge of the prevalence of clozapine genetic PMs is very limited. Less than 5% of patients of European ancestry and around 7% of patients of Asian ancestry (defined as ranging geographically from Afghanistan to Japan) may be genetic clozapine PMs (Ruan and de Leon, 2020). All the original inhabitants of the Americas, which in the US includes those called Native Americans and many of those called Hispanics, are descendants of East Asians and are likely to behave regarding clozapine metabolism as Asians (González-Esquivel et al., 2021).

The limited information suggests that CYP1A2 mutations vary based on ancestry. In patients with European ancestry, two CYP1A2 alleles with low or no activity have been described, CYP1A2*6 and CYP1A2*7 (Ruan and de Leon, 2020). In patients of Asian ancestry, several CYP1A2 alleles have been described as having no/limited function (CYP1A2*8, CYP1A2*11, CYP1A2*15 and CYP1A2*16). Each of these mutations were described in <1% of the Japanese samples (Ito et al., 2015). These alleles have not been studied in clozapine patients but may indicate genetic clozapine PM status in patients of Asian or American ancestry.

The clozapine titration guideline proposes weekly CRP levels during titration. This may be a relatively inexpensive and easy way to try to identify genetic clozapine PMs before they develop a serious clozapine-induced inflammation. In an Australian study of myocarditis, CRP elevations occurred at least 5 days before troponin elevations (Macneil et al., 2013). The first CRP level, measured in this patient on day 15, was abnormal and troponin was already elevated. We propose that it is likely that CRP on day 7 was already elevated. On the day when the dosage had been increased from 50 to 100 mg/day, there was already an improvement in psychosis, which is very unusual for this very small dose.

In summary, the clozapine titration guideline uses baseline and weekly CRP levels to identify patients who may be genetic clozapine PMs and need very small doses to reach a therapeutic response.

5. LIMITATIONS

This retrospective reinterpretation of previously published cases has been written after many years of studying the complex topic of clozapine-induced myocarditis. Only 3 cases are used to demonstrate to the reader how baseline and weekly CRP monitoring during clozapine titrations can be extremely helpful in personalizing titration in order to help prevent myocarditis. The limitations of this approach can only be understood after carefully considering the complexity and limitations of the articles in the area of clozapine-induced myocarditis. Most authors are not aware of the relevance of rapid titrations on clozapine-induced myocarditis. A 2021 article critically examined 12 previous comprehensive reviews of the topic published since 1999 and only 1 of the 12 supported the role of rapid titration (De Las Cuevas et al., 2022b). The same article explained that differences in DNA ancestry may explain the widely differing rates of myocarditis with incidences of 3% in Australia or Japan but much lower in some European countries that use very slow titrations, such as Denmark and the Netherlands (De Las Cuevas et al., 2021). Thus, these three cases with their limitations try to educate the reader concerning how 6 personalized clozapine titration guidelines may promote advancement in this area. A generic drug such as clozapine lacks funding support for prospectively testing these titrations in large multicenter studies and there is no funding to support the marketing of the 6 personalized titrations from these guidelines that are being disseminated by authors from 50 countries/regions (de Leon et al., 2022c). More recently, case reports of clozapine-induced fever associated with rapid titration have provided more detailed studies on the elevations of plasma cytokines (Nakamura & Nagamine, 2022).

6. FINAL DISCUSSION OF THE VALUE OF CRP MONITORING DURING CLOZAPINE TITRATION

If the baseline or prior CRPs were normal and then become abnormal during titration, this indicates: 1) clozapine-induced inflammation associated with too-rapid titration for the clozapine metabolism of that specific patient, and/or 2) co-occurrence of an infection, most frequently an upper respiratory infection.

In this situation 3 interventions are required: 1) consider whether to hold or stop the clozapine titration, 2) add more close monitoring with CRP and troponin, and 3) perform a thoughtful differential diagnosis.

The first decision after CRP becomes abnormal during titration is deciding whether clozapine titration should be stopped by holding the clozapine dose and not increasing it, or by discontinuing clozapine. If a co-infection exists, it may be better to stop clozapine and only restart it after the infection has disappeared and CRP has normalized. Once CRP is abnormal, close monitoring with daily CRP and troponin is recommended (Goldsmith & Cotes, 2017) until the situation has been resolved. A thorough and thoughtful differential diagnosis of the CRP elevation is needed since it only indicates that inflammation exists. Moreover, as the CRP value becomes abnormal, the released cytokines can inhibit clozapine metabolism. It is important to be very attentive to the risk, during an upper respiratory infection or any infection, that sedation, swallowing disturbances and/or hypersalivation may contribute to aspiration pneumonia (Schoretsanitis et al., 2021). The reader may want to consider reading an illustrative case of how clozapine dose reductions are important at any time during clozapine treatment, whether titrating or not, when a systemic infection develops in clozapine patients (McCollum et al., 2021). The clozapine titration guideline provides information on how to interpret clozapine levels during titration (de Leon et al., 2022c).

As illustrated by Case 2, clozapine-induced inflammation may coexist with an infection, which may contribute to CRP elevations during titration. As illustrated by Case 1, clozapine-induced inflammation may coexist with some other type of inflammations and contribute to elevations in CRP; this is why it is very important to obtain a baseline CRP level that is normal before starting clozapine. Finally, Case 3, which evolved from myocarditis in the first clozapine trial to DRESS in the rechallenge, illustrates that clozapine-induced myocarditis is the most frequent form of clozapine-induced inflammation but others are part of the same syndrome which can manifest with fever and/or other local inflammations including serositis, pneumonitis, hepatitis, pancreatitis, nephritis or colitis (Verdoux et al., 2019) or even any combination with skin abnormalities and eosinophilia, which is usually identified as DRESS (de Filippis et al., 2022).

In summary, this discussion encourages the reader to consider adding baseline and weekly CRP monitoring simultaneous with ANC monitoring during clozapine titration and exposes the reader to the 6 personalized titrations recently proposed (de Leon et al., 2022c). For those wanting to educate themselves on clozapine pharmacokinetics, a published comprehensive review that is free of charge is available (de Leon et al., 2020). We hope that this discussion of these 3 cases will increase the comfort level of community psychiatrists (Cotes et al., 2022) and other practitioners (Cotes et al., 2021) in the use of clozapine. The first prospective cases are starting to be published, but more are needed to verify this hypothesis. (Danilewitz et al., 2021; Kikuchi et al., 2022).

Acknowledgment: Lorraine Maw, M.A., at the Mental Health Research Center at Eastern State Hospital, helped with editing.

Funding: This article was completed without any external funding. No commercial organizations had any role in the writing of this paper for publication.

Competing interest: In the last 3 years, Aygün Ertuğrul has received speaker's honoraria from Abdi İbrahim Otsuka and Robert O. Cotes is a speaker for Clinical Care Options, has received research funding from Otsuka, Lundbeck, Roche, Alkermes, and has received consulting fees from Saladax Biomedical. In the last 3 years, Jose de Leon, Charles Shelton and Can-Jun Ruan report no conflicts of interest.

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Mérjük-e rutinszerűen a CRP-t a klozapin titrálása során? – Három eset tanulsága

Bevezetés: Egy friss nemzetközi ajánlás a következő megfontolásokat tartalmazza a személyre szabott klozapin titrálásra vonatkozóan: a 1. DNS alapú származást; 2. a dohányzás és nemi hovatartozást, valamint 3. a lassú metabolizáló státuszt (poor metabolizer, PM). Emellett a kiindulási és 4 hetes CRP-szint mérése javasolt. A túl gyors titrálás ugyanis egyes, speciális metabolizmussal rendelkező betegekben klozapinindukálta gyulladást és CRP-emelkedést idéz elő. **Módszerek:** Három publikált eset újraértelmezése az új ajánlás alapján. **Eredmények:** Az első esetben egy kínai nem dohányzó férfi szerepel, akinél a PM státusz miatt alakult ki gyulladás. A 2. esetben egy török nemdohányzó nőbetegnél alakult ki klozapinindukálta miokarditisz négy rizikófaktor hordozása miatt (lappangó gyulladás, obezitás, valproát és olanzapine együttes használata). A 3. esetben egy USA-ban élő, de európai (kaukázusi) származású, rizikófaktorokkal nem rendelkező férfibetegnél lépett fel miokarditisz rutin titrálás után. A gyógyszerszint mérés során azonban kiderült, hogy a betegnél PM státusz valószínű. A nemzetközi ajánlás alkalmazása segíthetett volna 1. az első esetben azzal, hogy emelkedett CRP-szint esetén nem javasolja a klozapin beállítást; a 2. esetben a négy rizikófaktor alapján javasolt lassabb titrálással; a 3. esetben a lehetséges PM státusz genetikai tesztelésével. **Konklúzió:** Klozapinbeállítás esetén, ha a normál tartományban lévő kiindulási, vagy megelőző CRP-szint a gyógyszer adagolása közben emelkedni kezd, ez arra utalhat, hogy 1. gyors titrálás mellett fellépő klozapinindukálta gyulladásra hajlamos a beteg; 2. a pácinesnél infekció zajlik. További prospektív vizsgálatok szükségesek ezeknek a feltevések igazolására.

Kulcsszavak: klozapin mellékhatás, klozapin vérszint, klozapin metabolizmus, CYP1A2, gyulladás, gyógyszerindukálta miokarditisz