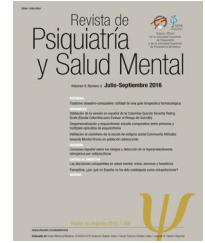




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BRIEF ORIGINAL

Valproate, obesity and other causes of clozapine poor metabolism in the context of rapid titration may explain clozapine-induced myocarditis: A re-analysis of a Turkish case series



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Abstract

Introduction: Clozapine-induced myocarditis or any clozapine-induced inflammation may be a hypersensitivity reaction due to titration that was too rapid for the patient's clozapine metabolism. Clozapine metabolism is influenced by ancestry, sex, smoking and the presence of confounders including obesity, infections, and inhibitors (e.g., valproate) causing the patient to behave as a clozapine poor metabolizer (PM). A published study in a Turkish hospital identified 1 case of clozapine-induced pancreatitis and hepatitis and 9 cases of clozapine-induced myocarditis. To explore the hypothesis that the 10 patients were clozapine PMs, their serum clozapine concentrations were investigated using concentration-to-dose (C/D) ratios and their titrations carefully reviewed.

Methods: Dividing the trough serum concentration by the dose produces the clozapine C/D ratio. The dose required to reach 350 ng/ml was considered the minimum therapeutic dosage and was used to classify patients according to clozapine PM status. Titration speed was assessed.

Results: All 10 patients were possibly clozapine PMs (3 of them had as minimum therapeutic doses: 72, 82 or 83 mg/day). Nine of the 10 patients may have behaved as clozapine PMs due to obesity and/or valproate co-prescription during titration. One also had an undiagnosed infection. Of the 10 patients, 9 had at least 1 of 3 factors: too-rapid titration in the first or second weeks, or a final dosage that was too high.

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Conclusions: Future studies using clozapine levels and considering the role of clozapine PM status should explore whether or not all cases of clozapine-induced inflammation could be explained by lack of individualized titration.

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PALABRAS CLAVE

Clozapina/administración y dosificación;
Clozapina/efectos adversos;
Clozapina/sangre;
Monitorización terapéutica;
Miocarditis/inducida químicamente

El valproato, la obesidad y otras causas de metabolismo deficiente de la clozapina en el contexto de una titulación rápida de las dosis pueden explicar la miocarditis inducida por clozapina: un nuevo análisis de una serie de casos turca

Resumen

Introducción: Cualquier inflamación inducida por la clozapina, incluida la miocarditis, podría ser una reacción de hipersensibilidad asociada a una titulación demasiado rápida de del fármaco para el metabolismo del paciente. El metabolismo de la clozapina está influenciado por la ascendencia, el sexo, el tabaquismo, y por la presencia de factores de confusión como obesidad, infecciones e inhibidores, como el valproato, que hacen que el paciente se comporte como un metabolizador lento (PM). Un estudio publicado identificó un caso de pancreatitis y hepatitis, y 9 casos de miocarditis inducidos por clozapina. Para explorar la hipótesis de que los 10 pacientes eran PM de clozapina, se investigaron sus concentraciones séricas de clozapina utilizando relaciones concentración/dosis (C/D) y revisando sus titulaciones.

Métodos: La dosis necesaria para alcanzar 350 ng/ml se consideró la dosis terapéutica mínima y clasificó a los pacientes según el estado de PM de clozapina. Se evaluó la velocidad de titulación.

Resultados: Los 10 pacientes eran posiblemente PM de clozapina (3 tenían dosis terapéuticas mínimas: 72, 82 u 83 mg/día). Nueve pacientes pueden haberse comportado como PM de clozapina debido a obesidad y/o prescripción conjunta de valproato durante la titulación. Uno también tenía una infección no diagnosticada. Nueve de los 10 pacientes tenían al menos uno de los 3 factores siguientes: titulación demasiado rápida en la primera o segunda semana, o una dosis final excesiva.

Conclusiones: Futuros estudios que utilicen niveles de clozapina y consideren el PM deberían explorar si la inflamación inducida por clozapina podría explicarse por la falta de titulaciones individualizadas.

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Introduction

Clozapine-induced myocarditis¹ or any clozapine-induced inflammation may be a hypersensitivity reaction due to titration that was too rapid for the patient's clozapine metabolism ([Supplementary Table S1](#)).²⁻⁴ Clozapine metabolism is influenced by ancestry, sex, smoking, or the patient's clozapine poor metabolizer (PM) status brought on by valproate co-medication, obesity, or infections ([Supplementary Table S2](#)).⁵⁻¹⁰

The hypothesis of PM status and rapid titration as a cause of myocarditis in clozapine users can be tested using the serum clozapine concentration-to-dose (C/D) ratios. We re-analyzed 9 cases of clozapine myocarditis which were found between 2011 and 2018 in a Turkish hospital¹¹ that fulfilled Ronaldson et al.'s criteria,¹⁰ and made available unpublished clozapine therapeutic drug monitoring (TDM). Another case with clozapine-induced inflammation (hepatitis and pancreatitis),¹² but no myocarditis, was identified in this Turkish study and included in this re-analysis of 10 cases of clozapine-induced inflammation⁴ during titration.

Methods

[Table 1](#) describes sex, smoking and body mass index (BMI), co-medication and daily clozapine dosing on days 1, 7, 14 and 21, and the stop day; further details are in [Supplementary Table S1](#). The clozapine C/D ratio in ng/ml per mg/day was calculated by dividing the trough serum concentration by the dose and provided an estimate of the dose required to reach 350 ng/ml,^{2,3,5,6,9} which was considered the minimum therapeutic dosage in that specific patient. [Table 2](#) defines whether or not the patients were clozapine PMs using [Supplementary Table S2](#), which summarizes all the available TDM data per patient and relates it to inflammation, sex, smoking and the presence of valproate or obesity. Based on recommendations for maximum titration from a textbook by Taylor et al.,¹³ [Supplementary Table S3](#) classifies (1) the titration increase in the first or second week (as mildly rapid, rapid, very rapid or extremely rapid) and (2) the final dose (as mildly high, high, very high or extremely high when compared with the patient's minimum therapeutic dose).

Table 1 Titration characteristics.

Case	Age sex smoking	BMI kg/ m ²	Comedication			Daily CLO D on day				Stop day (CLO D) ^a
			VPA (D in mg/d)	AP (D in mg/d)	Other (D in mg/d)					
						1	7	14	21	
1	65 yo ♀ unknown	25.3	Yes ^b	Que (25)	Li ^b	12.5	50	125		14 (125)
3	27 yo ♀ non-smoker	22.4	1000 mg/d	No	Li (900), Pro (20)	12.5	75	150		20 (200)
4	32 yo ♂ smoker	23.9	No	No	Li (900), Bip (2), Lor (2)	12.5	50	100		20 (125)
5	42 yo ♂ smoker	28.1	1500 mg/d	Ami (800)	Ser (50), Diaz (5)	12.5	75	250		16 (250)
6	23 yo ♂ non-smoker	31.0	No	Ami (800)	Li (1500), Preg (150)	25	150	300		18 (400)
7	48 yo ♀ smoker	29.0	No	Ola (15)	Bip (2)	25	100	250	300	22 (300)
8	19 yo ♀ non-smoker	36.4	1250 mg/d	Ola (15)	Bip (6), Clon (1)	12.5	50	200		20 (200)
9	52 yo ♂ non-smoker	27.8	1000 mg/d	Ris (5)	Bip (3)	25	75	150		19 (150)
10	23 yo ♂ non-smoker	29.0	1500 mg/d	Que (600)	Li (1200), Lor (1)	12.5	100	150		16 (150)
2	29 yo ♀ smoker	29.3	No	Ris (2)	No	12.5	75	300	300	34 (300)

Ami, amisulpride; AP, antipsychotic; Bip, biperiden; BMI, body mass index; Clon, clonazepam; D, dose; Diaz, diazepam; Li, lithium; Lor, lorazepam; Ola, olanzapine; Preg, pregabalin; Pro, propranolol; Que, quetiapine; Ris, risperidone; Ser, sertraline; VPA, valproic acid; yo: years of age.

^a This is the daily D on the day that it was stopped or the day before if the patient did not receive the full D on the day it was stopped.

^b Doses are unknown. This is the first patient who died and was not as well studied as the others. Moreover, the death of this patient led to the establishment of the myocarditis monitoring protocol.

Results

Description

In the 9 cases of clozapine-induced myocarditis, the clozapine discontinuation day ranged from 14 to 22 and the dose on that day from 125 to 400 mg/day. The tenth case (Case 2), a female smoker who presented with clozapine-induced hepatitis and pancreatitis at 300 mg/day of clozapine, was stopped on day 34.

All patients were at least possible clozapine PMs

Table 2 indicates that all have minimum therapeutic doses lower than the sex and smoking status group, which includes 3 cases of extremely PMs, 4 PMs and 3 cases of mildly PMs.

Case 1, who died, provided no information about smoking, so she was either a PM (non-smoker) or a mildly PM (for smoker), based on the estimated clozapine C/D ratio (Supplementary Table S4). Moreover, the calculation of Case 1s clozapine C/D ratio was problematic because it was done in the first week after only 5 days of treatment and with an average dose that was very low at 15 mg/day. This patient appeared to be a clozapine PM but it would have

been better to have more TDM for verification; however, she died on day 14.

Rapid titration and high final dose when compared with a personalized dose

During the first week there were 3 mildly rapid titrations, 2 rapid and 1 very rapid. In addition, during the second week, there were 6 mildly rapid titrations, 1 rapid, 1 very rapid and 1 extremely rapid. When comparing the minimum therapeutic dose in each patient, the final dose was mildly high in 4 cases, high in 1 case, very high in 2 cases and extremely high in 1 case.

All patients except Case 4 had, besides being clozapine PMs, at least one additional risk factor of rapid titration in the first or second week or a high final dose.

Nine patients with obesity, valproate and/or infection

The clozapine PM phenotype was possibly explained by: (1) valproate in 4 patients, (2) obesity in 3 patients, (3) the combination of valproate and obesity in 1 patient, and (4) the combination of valproate, obesity and infection in 1 patient.

Table 2 Final interpretation of the case^a

Clozapine PM			Titration increase		Overdose ^f (estimated D divided by final D)
Risk factors	Severity ^b	D for 350 ^c	First week ^d	Second week ^e	
1: VPA (non-smoker) (smoker)	Mildly PM PM	124 mg/day		Mildly rapid Mildly rapid	Mildly high Mildly high Mildly high
3: VPA	PM	141 mg/day	Mildly rapid		
4: None known	PM	141 mg/day			
5: VPA	Mildly PM	260 mg/day		Mildly rapid	
6: Obesity	Mildly PM	154 mg/day	Rapid	Mildly rapid	Very high
7: Obesity	Extremely PM	83 mg/day	Very rapid	Very rapid	Extremely high
8: VPA + obesity UTI	PM inflammation	130 mg/day		Rapid	High
9: VPA	PM	116 mg/day	Mildly rapid	Mildly rapid	Mildly high
10: VPA + obesity	Extremely PM	72 mg/day	Mildly rapid	Mildly rapid	Very high
2: Obesity	Extremely PM	85 mg/day	Rapid	Extremely rapid	Extremely high

^a Details for calculation are provided in [Supplementary Table S3](#).

^b The patients were compared with the stratified data from average patients of European ancestry (for reaching 350 ng/ml, the average patient needs 236 mg/day in female nonsmokers, 256 mg/day in male nonsmokers, 357 mg/day in female smokers, and 368 mg/day in male smokers).⁶ A clozapine mildly PM was one who needed $\frac{1}{2}$ to $\frac{3}{4}$ of the minimum therapeutic dose of the stratified group to reach 350 ng/ml. A clozapine PM was one who needed $\frac{1}{4}$ to $<\frac{1}{2}$ of the minimum therapeutic dose of the stratified group to reach 350 ng/ml. A clozapine extremely PM was one who needed $<\frac{1}{4}$ of the minimum therapeutic dose of the stratified group to reach 350 ng/ml.

^c The clozapine C/D ratio was used to estimate the dose required to reach 350 ng/ml which was considered the minimum therapeutic dosage in that specific patient.

^d Taylor et al.'s first week's titration provides an increase from 0 to 40% of their therapeutic dose for female non-smokers ([Supplementary Table S4](#)). Based on this recommended maximum titration (increase of 40%), [Supplementary Table S3](#) (footnote c) titration between 41 and 80% of the minimum therapeutic D for that specific patient was mildly rapid, a titration between 81 and 120% was rapid, and a titration > 120% was very rapid.

^e Taylor et al. suggest maximum second-week increases from 50 to 110% (increase of 60%) of their therapeutic dose for female non-smokers ([Supplementary Table S4](#)). [Supplementary Table S3](#) (footnote d) classifies the titration increase in the second week: between 61 and 120% of the minimum therapeutic D for that specific patient was mildly rapid, a titration between 120 and 180% was rapid, a titration between 181 and 240% was very rapid and a titration > 240% was extremely rapid.

^f [Supplementary Table S3](#) (footnote a) classifies the final dose that was 1.01–1.51-fold higher than the minimum therapeutic D for that specific patient as mildly high; a D 1.51–2.00 times higher than the minimum therapeutic D for that specific patient as high; a D between 2.01–3.00 times higher than the minimum therapeutic D as very high; and a dose > 3.00 times higher than the minimum therapeutic D as extremely high.

A patient with no known factors and no rapid titration

[Table 2](#) describes the perplexing Case 4, a male smoker who had no valproate or obesity and whose titration was very reasonable for its low minimum therapeutic dose of 141 mg/day to reach 350 ng/ml. He had had a CRP elevation since day 10, never had fever and the troponin test was normal. One possible explanation was that the patient was one of the genetic PMs and the clozapine was stopped before the whole symptomatic picture developed. The diagnostic cardiac ultrasound was done too late, 9 days after stopping clozapine on day 29 ([Supplementary Table S1](#)).

First abnormal CRP

[Supplementary Table S1](#) describes Case 8 as having CRP elevation from the first day due to a urinary tract infection. This further compromised clozapine metabolism in an obese patient taking valproate. She developed tachycardia, and on day 19 she had troponin elevation and a pericardial effusion. In the rest, CRP was the first sign of

clozapine-induced inflammation and the first abnormal CRP was identified from days 5 to 17. It is possible that CRP elevations would have been seen earlier if daily testing of CRP had been done instead of using a protocol of weekly CRP and troponin measures. In all patients CRP elevations happen several days before the troponin elevations.

Discussion

In spite of the limitations ([Supplementary Box S3](#)) this study found, as hypothesized, that all 10 patients with clozapine-induced inflammation were clozapine PMs in the context of inappropriate titrations.

Cases explained as a combination of clozapine PM status and lack of appropriate titration for them

The use of TDM indicated that all 10 patients were possibly clozapine PMs, including 3 who were called extreme PMs and only needed 72, 82 or 83 mg/day to reach a therapeutic dose in whom standard dosages and standard titrations were not

safe. Of the 10 patients, there were 9 who had at least 1 of 3 factors: too-rapid titration in the first week, too-rapid titration in the second week, or a final dosage that was too high.

Lessons from this study that may prevent future cases of clozapine-induced inflammation

Case 8, who had obesity and valproate co-prescription, also had baseline inflammation that could probably be explained by an undiagnosed infection even before starting clozapine. The first lesson is that no patient with abnormal CRP should be started on clozapine. The cause of the inflammation should be diagnosed and treated before starting clozapine.

Nine of 10 patients had obesity and/or valproate co-prescription that contributed to their behavior as clozapine PMs during the titration. The second lesson is that a patient taking valproate or with BMI > 29 kg/m² should be considered as a potential clozapine PM and started on a slower titration than the titration used in their ancestry group.¹⁴

All 9 patients, except Case 8 who had a baseline infection, developed CRP elevations several days before the final diagnosis, indicating that clozapine-induced inflammation was developing. Thus, whenever a CRP elevation occurs during titration the clozapine dose should be held and not increased until it has become normal again. At that time the dose can be increased again but it is very important to increase clozapine very slowly from that point on. Measuring CRP at least weekly with WBC and then daily at any sign of inflammation is extremely important in preventing severe cases of clozapine-induced inflammation. When CRP is abnormal it is important to frequently measure troponin, too, to explore the possibility of myocarditis even in patients with no obvious risk factors, as genetic clozapine PMs exist. When CRP becomes abnormal during clozapine titration, daily monitoring of CRP and troponin is recommended.¹⁴ It is possible Case 4 was a genetic PM. Studies are needed to explore which rare CYP1A2 alleles may explain genetic clozapine PMs in people from different ancestries.

Studies of clozapine titrations in countries which appear to neglect clozapine-induced myocarditis are needed including countries with no unawareness of the diagnosis (e.g., Russia¹⁵) and those with low numbers of diagnoses despite people with decreased clozapine metabolism (Asia and American countries with Amerindians⁵).

In summary, the three lessons are: (1) use baseline CRP to rule out an undiagnosed inflammation; (2) use slower titrations for potential clozapine PMs, such as those with obesity or taking valproate, and (3) measure weekly CRP and pay careful attention to CRP elevations and other signs of inflammation, such as fever. These are relatively easy and inexpensive measures for preventing myocarditis.¹⁴

Conclusions

Future studies will need to verify this re-analysis of a case-series which suggests that all the patients were clozapine PMs and most of them may have had titrations that were too fast for their ability to metabolize clozapine. To prevent myocarditis, titrations considering ancestry, sex, smoking

status and the presence or absence of obesity, inhibitors and inflammation can be used.¹⁴

Authors' contributions

The original study was published by all the Turkish authors: AE, AEAY, EA, AAK, SA, and MKY. JdL approached the Turkish authors in order to analyze the clozapine levels that were not included in the first article. JdL designed the analyses and the methodology based on the available data. AE and AEAY verified JdL's calculations. JdL drafted the initial version of the manuscript. All authors reviewed the initial draft and made critical contributions to the interpretation of the data and approved the manuscript.

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Conflict of interest

No commercial organizations had any role in writing this paper for publication. In the past 3 years, AE has received speaker's honoraria from Abdi İbrahim Otsuka and AEAY has received speaker's honoraria from and consulting fees for Janssen and Abdi İbrahim Otsuka. The remaining authors had no commercial conflicts of interest in the past 3 years.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.rpsm.2021.10.003>.

References

- De las Cuevas C, Sanz EJ, Norén N, Ruan CJ, de Leon J. Clozapine-associated myocarditis in the World Health Organization's pharmacovigilance database: focus on reports from various countries. *Rev Psiquiatr Salud Ment.* 2021; <http://dx.doi.org/10.1016/j.rpsm.2021.07.004>. S1888-9891(21)00070-7.
- de Leon J, Rhee DW, Kondracke A, Diuguid-Gerber J. Rapid titration and decreased clozapine clearance may help explain five cases of clozapine-induced myocarditis in a New York hospital. *Psychosomatics.* 2020;61:102–3, <http://dx.doi.org/10.1016/j.psych.2019.08.008>.
- de Leon J, Ruan CJ, Schoretsanis G, De Las Cuevas C. A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. *Psychother Psychosom.* 2020;89:200–4, <http://dx.doi.org/10.1159/000507638>.
- Verdoux H, Quiles C, de Leon J. Clinical determinants of fever in clozapine users and implications for treatment management: a narrative review. *Schizophr Res.* 2019;211:1–9, <http://dx.doi.org/10.1016/j.schres.2019.07.040>.

5. González-Esquivel DF, Jung-Cook H, Baptista T, de Leon J. Amerindians may need clozapine dosing similar to that of Asians. *Rev Psiquiatr Salud Ment.* 2021;14:177–9, <http://dx.doi.org/10.1016/j.rpsm.2020>.
6. Schoretsanitis G, Smith RL, Molden E, Solismaa A, Seppälä N, Kopeček M, et al. European Caucasians may need lower minimum therapeutic clozapine doses than those customarily proposed. *J Clin Psychopharmacol.* 2021;41:140–7, <http://dx.doi.org/10.1097/JCP.0000000000001341>.
7. Ruan CJ, de Leon J. Is there a future for CYP1A2 pharmacogenetics in the optimal dosing of clozapine? *Pharmacogenomics.* 2020;21:369–73, <http://dx.doi.org/10.2217/pgs-2020-0015>.
8. de Leon J. Future studies on the interaction between clozapine and valproic acid should aspire to include longitudinal designs and free valproate concentrations, and should consider that inducer and/or inhibitory effects may vary with time, the individual, and the auto-induction of valproic acid. *Ther Drug Monit.* 2020;42:159–61, <http://dx.doi.org/10.1097/FTD.0000000000000705>.
9. Ruan CJ, Zang YN, Cheng YH, Wang CY, de Leon J. Around 3% of 1300 levels were elevated during infections in a retrospective review of 131 Beijing hospital in-patients with more than 24,000 days of clozapine treatment. *Psychother Psychosom.* 2020;89:255–7, <http://dx.doi.org/10.1159/000506355>.
10. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust NZ J Psychiatry.* 2011;45:458–65, <http://dx.doi.org/10.3109/00048674.2011.572852>.
11. Anıl Yağcıoğlu AE, Ertuğrul A, Karakaşlı AA, Ağaoğlu E, Ak S, Karahan S, et al. A comparative study of detection of myocarditis induced by clozapine: with and without cardiac monitoring. *Psychiatry Res.* 2019;279:90–7, <http://dx.doi.org/10.1016/j.psychres.2019.07.008>.
12. Yildiz MI, Karacam Dogan M, Mutlu E, Abdullayeva L, Ozmen F, Ertugrul A. All in one: clozapine-associated acute pancreatitis with multiple organ involvement. *J Clin Psychopharmacol.* 2021;41:214–6, <http://dx.doi.org/10.1097/JCP.0000000000001365>.
13. Taylor DM, Barnes TRE, Young AH. *Maudsley prescribing guidelines in psychiatry.* 13th ed. Hove, UK: Wiley-Blackwell; 2018.
14. de Leon J, Schoretsanitis G, Smith RL, Molden E, Solismaa A, Seppälä N, et al. An international adult guideline for making clozapine titration safer by using 6 ancestry-based personalized dosing titrations, CRP and clozapine levels. *Pharmacopsychiatry.* 2022, <https://doi.org/10.1055/a-1625-6388>.
15. Kirilochev OO, Cuevas CL, de Leon J. Clozapine-induced myocarditis in Russia: animal studies but no clinical studies. *Rev Psiquiatr Salud Ment.* 2021, <http://dx.doi.org/10.1016/j.rpsm.2021.09.001>. S1888-9891(21)00100-2.