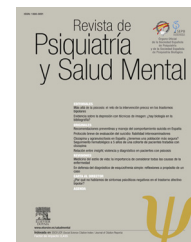




# Revista de Psiquiatría y Salud Mental

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## BRIEF REPORT

# Concentrations in plasma clozapine levels in schizophrenic and schizoaffective patients<sup>☆</sup>

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Received 27 January 2017; accepted 27 June 2017

### KEYWORDS

Clozapine;  
Norclozapine;  
Plasma level  
monitoring;  
Resistant  
schizophrenia

### Abstract

**Introduction:** There is great variability in plasma levels of clozapine. The objective of this study is to know the characteristics of patients treated with clozapine and the relationship between them and the variability of plasma levels.

**Material and methods:** Descriptive, cross-sectional study of all patients currently treated with clozapine in a Psychiatric Service with a diagnosis of schizophrenic psychosis or schizoaffective disorder. The present study assessed physical situation, psychopathology and functionality of the patients and explored the associations and correlations between clinical variables and plasma levels.

**Results:** We studied 39 patients, predominantly men, with negative and depressive symptoms and cardiovascular risk factors (metabolic syndrome and smoking). Significant variability in dose and even greater in clozapine levels were observed. The levels of clozapine at equal doses/kg of body weight were higher in non-smokers, they had positive correlation with BMI and negative correlation with systolic BP, disruptive behaviours and number of cigarettes consumed.

**Conclusion:** Plasma level monitoring clozapine is an important tool to avoid clozapine plasma levels monitoring and minimise undesirable clinical situations (metabolic syndrome, sedation, negative symptoms and functional impairment). It is also important to control the effects of a smoking habit for optimum drug bioavailability.

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<sup>☆</sup> Please cite this article as: Iglesias García C, Iglesias Alonso A, Bobes J. Variaciones en las concentraciones plasmáticas de clozapina en pacientes con esquizofrenia y trastorno esquizoafectivo. Rev Psiquiatr Salud Ment (Barc.). 2017. <https://doi.org/10.1016/j.rpsm.2017.06.002>

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**PALABRAS CLAVE**

Clozapina;  
Norclozapina;  
Concentraciones  
plasmáticas;  
Esquizofrenia  
resistente

**Variaciones en las concentraciones plasmáticas de clozapina en pacientes con esquizofrenia y trastorno esquizoafectivo****Resumen**

*Introducción:* Existe mucha variabilidad en las concentraciones plasmáticas de clozapina. El objetivo de este trabajo es conocer las características de pacientes tratados con clozapina y la posible asociación entre estas y las concentraciones plasmáticas.

*Material y métodos:* Estudio descriptivo y transversal de todos los pacientes actualmente tratados con clozapina en un Servicio de Psiquiatría con diagnóstico de psicosis esquizofrénica o trastorno esquizoafectivo. Se valoró la situación física, psicopatología y funcionalidad, y se exploraron las asociaciones y correlaciones entre las variables clínicas y las concentraciones plasmáticas.

*Resultados:* Se estudiaron 39 pacientes, predominantemente hombres, con sintomatología negativa, síntomas depresivos y factores de riesgo cardiovascular (síndrome metabólico y consumo de tabaco). Se observó variabilidad importante en las dosis y mayor aún en las concentraciones plasmáticas de clozapina. A igualdad de dosis/kg de peso las concentraciones plasmáticas fueron más altas en no fumadores, y presentaron correlación positiva con el IMC y correlación negativa con la PA sistólica, conductas disruptivas y cantidad de cigarrillos consumidos.

*Conclusión:* La monitorización de concentraciones plasmáticas de clozapina es un instrumento importante para evitar la variabilidad de dosis y minimizar situaciones clínicas no deseadas (síndrome metabólico, sedación, síntomas negativos y deterioro funcional). Es importante controlar los efectos del consumo de tabaco para la optimización de la biodisponibilidad del fármaco.

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**Introduction**

Clozapine is an antipsychotic drug with a complex pharmacodynamic profile. It has been shown to be more effective than the other first and second generation antipsychotic drugs in the treatment of resistant schizophrenia.<sup>1</sup> It is fundamentally metabolised by the hepatic microsomal enzymes CYP1A2 and CYP3A4, and one of its 2 main metabolites, the desmethyl metabolite N-desmethyl-clozapine (norclozapine) is pharmacologically active. Plasmatic concentrations of clozapine are highly variable and depend on absorption, hepatic metabolism and other factors such as nicotine, age and sex.<sup>2</sup> The determination of plasmatic concentrations of clozapine and norclozapine are used to evaluate compliance with the therapy, to optimise treatment and to minimise the risk of adverse effects.<sup>3</sup> In spite of the therapeutic importance of the drug and the severity of the patients who receive it, there are few studies of plasmatic concentrations of clozapine. The aims of this work are: to examine the clinical situation of patients treated with clozapine, the doses and plasmatic concentrations of the same and the possible association between plasmatic concentrations and patient characteristics.

**Material and methods**

This is a descriptive transversal study of all the patients currently treated with clozapine in a Psychiatry Department with the diagnosis of schizophrenic psychosis or schizo-affective disorder. The diagnosis was made by the psychiatrist in charge of the case, according to CIE-10 criteria. The study

was approved by the Local Clinic Research Ethics Committee and it took place according to the norms of good clinical practice. The specific norms governing the use of clozapine were followed in all cases. Additionally, the patients diagnosed schizo-affective disorder who were taking clozapine without indication did so on prescription by the psychiatrist in charge of their case following the consideration that other psychopharmacological resources had been exhausted and that this complied with legal requisites (RD 1015/2009, of 19 June). Prior to undertaking this study no systematic determination of plasmatic concentrations of clozapine had been systematically undertaken.

Sociodemographic and clinical variables were studied, together with anthropometric measurements, life signs, haemogram and metabolic parameters. Plasmatic concentrations of clozapine and norclozapine were determined (this took place while fasting in the morning, without having eaten during the night or taken the breakfast dose of clozapine). Psychopathological examination covered the following areas: psychotic symptoms on the PANNS<sup>4</sup> scale; cognition on the SCIP<sup>5</sup> scale; functionality on the PSP<sup>6</sup> scale and depressive symptoms on the Phq-9<sup>7</sup> scale.

The categorical variables are described using their frequencies and percentages, while continuous variables are described using their averages and standard deviations (SD). Differences between groups are compared using the chi-squared test or Fisher's exact test when a group smaller than 5 was found. In the case of continuous variables, to compare differences between the averages among groups the Student's *t*-test was used for two independent samples, or analysis of variance (ANOVA) in the case of 3 or more groups. Pearson's correlation coefficient was

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