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ORIGINAL ARTICLE

Increase in white cell and neutrophil counts during the first eighteen weeks of treatment with clozapine in patients admitted to a long-term psychiatric care inpatient unit☆

Adrián Capllonch*, Silvia de Pablo, Alberto de la Torre, Ignacio Morales

Complejo Asistencial Benito Menni, Unidad de Cuidados Psiquiátricos Prolongados, Ciempozuelos, Madrid, Spain

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KEYWORDS
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Abstract
Introduction: Clozapine is an antipsychotic drug that has shown to be more effective than other antipsychotics in the treatment of schizophrenia, but its use is limited due to its side effects, particularly by the risk of causing agranulocytosis. A study was made on the variations in white cell and neutrophil counts in patients treated with Clozapine in a Long-term Psychiatric Unit.
Methods: A retrospective observational study was conducted with a sample of women of our long-term psychiatric care unit who had been treated with Clozapine. A study was made on the variations in white cell and neutrophil counts during the first 18 weeks of treatment, as well as the onset of leukopenia, neutropenia, agranulocytosis, and the influence of concomitant drugs.
Results and conclusions: The study included 55 patients on treatment with Clozapine. The incidence rate of neutropenia was 1.82% (95% CI: 0.05–10.13). The incidence rate of leukopenia and agranulocytosis was 0%. An increase in white cell and neutrophil counts from baseline to week 3–4 was observed. Only small variations were observed after this time, but the counts remained higher than the initial values. These changes were statistically significant in the white cell count: One-way repeated ANOVA with Greenhouse–Geisser correction F (11.47, 37) = 2.114 (P = .011); and in neutrophils: One-way repeated ANOVA with Greenhouse–Geisser correction F (10.3, 37) = 3.312 (P = .0002), and MANOVA F (18, 37) = 2.693 (P = .005), $\eta_p^2 = 0.567$. The influence of concomitant drugs (lithium, valproic and biperiden) was not significant on the overall increase found in white cells or neutrophils (MANOVA).

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* Corresponding author.
E-mail address: adriancapllonch@gmail.com (A. Capllonch).

PALABRAS CLAVE
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Aumento en los recuentos de leucocitos y neutrófilos durante las primeras 18 semanas de tratamiento con clozapina en pacientes ingresadas en una unidad de cuidados psiquiátricos prolongados

Resumen
Introducción: La clozapina es un antipsicótico que ha demostrado mayor eficacia que el resto de antipsicóticos en el tratamiento de la esquizofrenia, pero su uso está restringido por sus efectos secundarios, especialmente por su riesgo de agranulocitosis. Nos propusimos estudiar las variaciones en los leucocitos y neutrófilos en pacientes en tratamiento con clozapina e ingresadas en hospitalización psiquiátrica prolongada.
Material y métodos: Se estudió una muestra de mujeres ingresadas en nuestra UCPP y en tratamiento con clozapina. Se estudió la variación de los recuentos de leucocitos y neutrófilos durante las primeras 18 semanas de tratamiento, la aparición de leucopenia, neutropenia y agranulocitosis, así como la influencia de los fármacos empleados de forma concomitante.
Resultados y conclusiones: Se obtuvo una tasa de incidencia de neutropenia de 1,82% (IC 95%: 0,05-10,13) y ningún caso de leucopenia ni agranulocitosis (0%). En el análisis cuantitativo de leucocitos y neutrófilos durante las 18 semanas de tratamiento, se observó un aumento hasta la semana 3-4, tendiendo después a la estabilización de las cifras alcanzadas, pero manteniendo siempre cifras superiores a las de los valores iniciales. Estas diferencias resultaron estadísticamente significativas para los leucocitos en el ANOVA de medidas repetidas con la corrección de Greenhouse-Geisser F (11,47, 37) = 2,114 (p = 0,011), η^2_P = 0,038. También resultó significativo para los neutrófilos el ANOVA con la corrección de Greenhouse-Geisser F (10,33, 37) = 3,312 (p = 0,0002), y el MANOVA F (18, 37) = 2,693 (p = 0,005), η^2_P = 0,567). La influencia de los fármacos estudiados de forma concomitante (litio, valproico y biperideno) no resultó globalmente significativa (MANOVA) sobre el aumento hallado en los leucocitos y neutrófilos.

Introduction

Clozapine is the only drug indicated specifically for the treatment of treatment-refractory schizophrenia. It has been shown to achieve a greater improvement than other antipsychotic drugs for positive, negative and cognitive symptoms. Its side effects profile means that its role as the first line antipsychotic in first-time neuroleptic treatment patients is questionable. Nevertheless, over the years major variations have been observed in different populations in the risk of Clozapine-induced agranulocytosis. The appearance of agranulocytosis seems to be a non-dose dependent side effect, and although there are different hypotheses about its physiopathology and possible associations with other trigger factors,[1] conclusive data are still lacking. Although the initial studies found an incidence of agranulocytosis of from 1% to 2%,[2] subsequent studies undertaken after the introduction of monitoring of leucocyte and neutrophil counts have shown a lower risk. In this respect it is more similar to other antipsychotic drugs (one study performed in Spain from 1993 to 1998 calculated an incidence of 0.2% during the first 3 years of treatment, CI 95%: 0.1–0.6).[3] Given that patients with treatment-refractory schizophrenia form a large proportion of patients with prolonged psychiatric hospitalisation, and given the lack of specific data on the haematological effects of Clozapine in this population, we decided to study the variations in leucocyte and neutrophil counts in patients with these characteristics.

Material and methods

Our study has an observational, analytical, longitudinal and retrospective design, with repeated measurements of white cell and neutrophil counts during the first 18 weeks of treatment with Clozapine. A sample of women admitted to a long-term psychiatric care unit (LTPCU) of the Complejo Asistencial Benito Menni, Ciempozuelos (Madrid) was selected on 31 December 2012. They were treated with Clozapine during admission, and were selected independently of their age, clinical diagnosis, reason for commencing treatment or other variables. The exclusion criteria were: having started treatment with Clozapine prior to admission in the unit, or presenting an incomplete protocol of haematological monitoring due to an error in compliance (but not if the interruption were for a clinical reason). Patient sociodemographic data were collected during the study, including their age and psychiatric diagnoses coded according to the CIE-10.

To gather data the haematological monitoring checks during follow-up were used (according to the regulations in force[4]). In our case data gathering was restricted to the basal count (prior to starting Clozapine treatment) and the count after the first 18 weeks of treatment. The dose of Clozapine administered each week to each patient was recorded, together with the doses of the other drugs administered to each patient concomitantly. The period of time during which these counts took place