

ANALYSIS OF CLOZAPINE AND NORCLOZAPINE CONCENTRATIONS IN ADULT PATIENTS WITH SCHIZOPHRENIA

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The atypical antipsychotic clozapine (*CLZ*) is primarily used for the treatment-resistant schizophrenia. Due to low therapeutic index and high pharmacokinetic variability, therapeutic drug monitoring (*TDM*) is highly recommended (1). The aim of this retrospective study was to analyze *TDM* data of *CLZ* and its active metabolite norclozapine (*NCLZ*) in adult patient with schizophrenia. The study included *CLZ TDM* data obtained from 69 patients (22-67 years) treated at the Clinic for Psychiatry, Clinical Center of Serbia, while *NCLZ* data were available from 43 patients. Serum concentrations were determined at the Institute of Forensic Medicine, Belgrade, Serbia using liquid chromatography with tandem mass spectrometry (*LC-MS/MS*). Statistical analysis was performed by SPSS software® (version 18). The daily doses of *CLZ* ranged between 37.5 and 600 mg. The mean value of *CLZ* and *NCLZ* levels were 0.285 ± 0.174 mg/L and 0.189 ± 0.132 mg/L, respectively. 73.06% and 26.83% of measured *CLZ* and *NCLZ* concentrations were outside reference range (mostly below), respectively. Significant positive correlation ($p < 0.05$) was observed between daily dose and *CLZ* levels, as well as between dose and *NCLZ* levels. Significant correlations of dose and *CLZ* levels were confirmed in males and females, smokers and nonsmokers, separately. Parent drug and metabolite levels varied 13 and 16-fold in patients receiving 300 mg/day, respectively. The results indicate considerable variability in *CLZ* and *NCLZ* concentrations in adult patients with schizophrenia, and positive association with dose. Further multivariate analysis is required to assess, in addition to dose, potential influences of other patient and co-therapy factors.

References

1. Hiemke C et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. *Pharmacopsychiatry* 2018; 51: 9-62.

ANALIZA KONCENTRACIJA KLOZAPINA I NORKLOZAPINA KOD ODRASLIH PACIJENATA SA SHIZOFRENIJOM

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Atipični antipsihotik klozapin (*clozapine, CLZ*) se primarno koristi kod shizofrenije rezistentne na terapiju. Zbog niskog terapijskog indeksa i velike farmakokinetičke varijabilnosti, terapijsko praćenje lekova (*therapeutic drug monitoring, TDM*) se preporučuje (1). Cilj ovog retrospektivnog istraživanja je bio ispitivanje *TDM* podataka o *CLZ* i njegovom aktivnom metabolitu norklozapinu (*norclozapine, NCLZ*) kod odraslih pacijenata sa shizofrenijom. Studija je obuhvatila *TDM* podatke o *CLZ* dobijene od 69 pacijenata (22-67 godina) lečenih na Klinici za psihijatriju Kliničkog centra Srbije, dok su podaci za *NCLZ* bili dostupni od 43 pacijenta. Koncentracije u serumu su merene na Institutu za sudsku medicinu, Beograd, Srbija tačnom hromatografijom sa tandem masenom spektrometrijom (*LC-MS/MS*). Statistička analiza je izvršena pomoću softvera SPSS® (verzija 18). Dnevne doze *CLZ* kretale su se između 37,5 i 600 mg. Srednja vrednost je bila $0,285 \pm 0,174$ mg/L za *CLZ* i $0,189 \pm 0,132$ mg/L za *NCLZ*. 73,06% i 26,83% izmerenih koncentracija *CLZ* i *NCLZ* bile su izvan referentnog opsega (uglavnom ispod), respektivno. Detektovana je pozitivna korelacija ($p < 0,05$) između dnevne doze i nivoa *CLZ*, kao i doze i nivoa *NCLZ*. Značajna korelacija doze i nivoa *CLZ* je potvrđena i pri odvojenom ispitivanju kod muškaraca, žena, pušača i nepušača. Nivoi leka i metabolita varirali su 13 i 16 puta kod pacijenata koji su uzimali 300 mg/dan, respektivno. Rezultati ukazuju na značajnu varijabilnost u koncentracijama *CLZ* i *NCLZ* kod odraslih pacijenata sa shizofrenijom i pozitivnu povezanost sa dozom. Potrebna je dalja multivarijantna analiza da bi se procenili, pored doze, potencijalni uticaji karakteristika pacijenata i kombinovane terapije.

Literatura

1. Hiemke C et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. *Pharmacopsychiatry* 2018; 51: 9-62.