Establishing therapeutic plasma clozapine concentrations in older people

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Abstract

Aims: There is no specific guidance on optimal clozapine plasma concentrations in older people. This study aimed to test the hypothesis that therapeutic plasma clozapine concentrations would be lower in patients with an onset of psychosis after 60 years, compared to those with an earlier onset of schizophrenia (EOS) and to investigate the relationship between pharmacokinetic indices and side effects. Methods: Data were extracted from anonymised healthcare records for clozapine treated patients aged over 55 years. Median plasma clozapine and norclozapine concentrations (Cclozapine, Cnorclozapine) were compared across diagnostic groups. Mixed-effects models were used to investigate the relationship between pharmacokinetic biomarkers and side effects. Results: Of the 481 patients (4519 samples, median 6 per person), 430 (89.4%) were diagnosed with EOS. Cclozapine and Cnorclozapine in those with Parkinson's disease psychosis (0.17mgL-1, 0.08mgL-1) were lower than those with EOS (0.41mgL-1, 0.19mgL-1), dementia-related psychosis (0.40mgL-1, 0.24mgL-1) and very late-onset schizophrenia-like psychosis (0.42mgL-1, 0.17mgL-1). Cclozapine was associated with higher corrected QT interval (QTc), whilst Cclozapine and Cnorclozapine were associated with higher neutrophil counts and body mass index, but not with clinical thresholds for neutropenia, obesity, QTc prolongation, or with sedation. Conclusions: Our findings suggest that, compared to EOS, therapeutic plasma clozapine concentrations are lower in Parkinson's disease psychosis but not in other forms of later onset psychosis. Interpretation was limited by the relatively young age of the sample and the small number of samples associated with side effects. Prospective studies are needed to further explore optimal dosing specifically in older people.

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