The relationship between plasma clozapine concentration and clinical outcome: a cross-sectional study

Abstract:

Objective: There is no report that statistically evaluates the therapeutic reference (350–600 ng/mL) and adverse drug reaction (ADR) range (>1000 ng/mL) of clozapine (CLZ) recommended by the *Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP)* consensus guidelines in an isolated and large sampling study.

Methods: We administered CLZ to 131 Japanese patients with treatment-resistant schizophrenia in a multicenter cross-sectional study. Plasma CLZ concentrations were assayed by high-performance liquid chromatography using trough sampling. The Brief Psychiatric Rating Scale (BPRS) and severe dose-dependent ADR (sedation, myoclonus, and seizures) were analyzed statistically after adjusting for possible confounders.

Results: The daily CLZ dosage showed a moderately positive relationship with the plasma concentration (r = 0.49, p <0.001). Every 100 ng/mL increase in plasma CLZ concentration improved the total BPRS score 1.95% (95% CI: 0.89–3.01, p <0.001) and the odds ratio (OR) 1.38 (95% CI: 1.14–1.66, p = 0.001) for BPRS response. Compared with concentrations below 350 ng/mL CLZ, 350–600 ng/mL (11.12%; 95% CI: 2.52–19.72, p = 0.012) and 600–1000 ng/mL (11.05%; 95% CI: 2.40–19.71, p = 0.013) showed significant improvement in the total BPRS score. Dosages above 1000 ng/mL showed greater improvement (25.36%; 95% CI: 13.08–37.64, p <0.001) of the total BPRS score but more severe ADRs than dosages below 1000 ng/mL (OR: 31.72; 95% CI: 1.04–968.81, p = 0.048).

Conclusion: The AGNP therapeutic reference range (350–600 ng/mL) is useful, and a dose above 1000 ng/mL is potentially more effective but carries the risk of severe ADRs in the central nervous system.