PHARMACOKINETICS OF PALIPERIDONE IN PATIENTS WITH SCHIZOPHRENIA: COMPARISON BETWEEN ORAL AND LONG-ACTING INJECTION FORMULATIONS

Vincenza Santoro[1], Edoardo Spina[1], Antonio Bruno[2], Sara Baldelli[3], Emilio Clementi[4], Dario Cattaneo[3]

[1]Dipartimento di Medicina Clinica e Sperimentale, Messina - Italy, [2]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, Messina - Italy, [3]Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco University Hospital, Milan - Italy, [4]Department of Biomedical and Clinical Sciences, L. Sacco University Hospital, 5Unit of Clinical Pharmacology, Scientific Institute, IRCCS E. Medea, Milan - Italy

Introduction: Paliperidone is a second-generation antipsychotic widely used in the treatment of schizophrenia and related psychotic disorders. It is marketed as an oral and long-acting injectable (LAI) formulation. According to the updated consensus guidelines for therapeutic drug monitoring (TDM) in neuropsychopharmacology, the paliperidone therapeutic reference range is 20-40 ng/mL. Aim of the present study was to evaluate differences in the pharmacokinetics of paliperidone between oral and LAI formulations using a large TDM database.

Materials and methods: From a TDM database containing serum concentrations of paliperidone collected between 2012and 2018, two separate groups of patients were considered, those treated with oral paliperidone and those on LAI paliperidone. In the case of multiple available serum concentrations for a single patient, only the most recent value was included in the analysis. Steady-state was defined as ≥ 5half-lives in the oral group and ≥ 5injections in the LAI group. The daily dosage of paliperidone in the LAI group was calculated by dividing the depot dose by 28, the number of days in the depot interval. Serum concentrations of paliperidone were measured by high-performance liquid chromatography.

Results: After the exclusion of patients on potentially confounding co-medications or with hepatic/renal impairment, 202patients (114males and 88females, aged 22to 64years) met the inclusion criteria, including 53in the oral paliperidone group and 149in the LAI paliperidone group. In the oral group serum concentrations of paliperidone ranged from 8to 99ng/mL (mean ± SD = 32.8± 11.4ng/mL), while in the LAI group from 4to 94ng/mL (29.3± 12.4ng/mL). As the daily dosage of paliperidone was lower in the LAI group, the concentration-to-dose ratio (C/D ratio) was used for comparison. The C/D ratio of paliperidone was higher in the LAI than in the oral group (7.3± 2.7vs 4.2± 1.8ng/mL per mg/day; $p<0.001$). The percentage of patients with subtherapeutic levels was significantly higher ($p<0.01$) in the LAI group (32.2%) as compared to the oral one (20.7%).

Discussion and conclusion: Our findings indicate that oral and LAI paliperidone formulations show different pharmacokinetic characteristics. The lower paliperidone C/D ratio after the oral formulation is presumably related to first-pass metabolism and lower compliance. Interestingly, a higher percentage of patients in the LAI group had serum paliperidone concentrations below the reference range suggested by consensus guidelines. As these patients were clinically stable, these findings suggest that therapeutic ranges of newer antipsychotics may be slightly different according to pharmaceutical formulations and, therefore, especially for LAI, should be better defined.