Pharmacokinetic Analysis of Antipsychotics in Elderly Patients with Delirium Using Nonlinear Mixed-Effects Modeling

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Introduction: The incidence of delirium in acute care hospitals is considerable, ranging from 30% to 82% in intensive care units, particularly among older, more vulnerable patients. It has far-reaching consequences, including higher mortality, long-term cognitive impairment, and increased healthcare expenses. Despite widespread off-label use of antipsychotics, there are still no comprehensive, recognized approaches that are effective for delirium therapy in elderly patients. The pharmacokinetics of antipsychotics significantly change in elderly individuals, which complicates treatment. This experimental investigation examined the capillary blood levels of pipamperone and risperidone in elderly patients with delirium.

Methods: From January 2021 to April 2022, a prospective observational study was conducted in four German hospitals. Risperidone and pipamperone capillary blood samples were collected from elderly hospital patients by therapeutic drug monitoring (TDM). The impacts of patient-specific variables and pharmacokinetics were evaluated using the nonlinear mixed-effects modeling software NONMEM®. Capillary blood samples were obtained with VAMS™ methods and analyzed using high-performance liquid chromatography-mass spectrometry (HPLC-MS).

Results: Fifty samples of risperidone from 17 patients and fifty-two pipamperone samples from 16 patients were collected during delirium therapy. Using external data from a single-dose study including 71 genotyped healthy volunteers, a 1-compartment (1-CMT) model in NONMEM® was developed using 3,365 plasma blood concentrations of risperidone. The 1-CMT model for pipamperone showed a volume of distribution (Vd/F) of 550 L and an oral population clearance (CL/F) of 36.1 L/h, whereas for risperidone, a Vd/F of 117 L was estimated along with a total CL/F of 35.4 L/h. The CYP2D6 phenotype significantly affected the oral clearance of risperidone with an interindividual variability of 78.7% on CL/F.

Conclusion: This study provides the first population-based pharmacokinetic models for pipamperone and risperidone in elderly delirium patients. Pharmacotherapy for individuals with delirium can be optimized through additional research on the unique pharmacokinetics of these antipsychotics. This study enhances our understanding of interindividual variability in pipamperone and risperidone pharmacokinetics, thereby improving the safety of delirium treatment in elderly patients.

Keywords: pharmacokinetics, antipsychotics, delirium, elderly, nonlinear mixed-effects modeling, therapeutic drug monitoring