Using Bayesian Modeling to Optimize Antipsychotic Therapy

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Objective: Population models exist for risperidone[1] and olanzapine[2], two commonly used atypical antipsychotics for treatment of schizophrenia. There are published relationships between these antipsychotics and dopamine D₂ receptor occupancy[3] as well as receptor occupancy and treatment outcomes[4]. These relationships make the drugs prime candidates for therapeutic drug monitoring. The objective was to develop a simple to use, yet robust and accurate, clinical tool allowing physicians to optimize antipsychotic therapy after sparse sampling.

Methods: Patients were dosed to steady-state on either risperidone or olanzapine and two plasma concentrations taken. After dose adjustment, a [¹¹C]-raclopride PET scan was performed to measure D₂ receptor occupancy and a third steady state concentration was taken at the time of scan. Population models were implemented using "mrgsolve"[5] and PK parameters were optimized using gradient descent to minimize MAP Bayes objective function. “Shiny”[6] package was used to develop user interface. Only first two plasma concentrations were used in optimization of MAP Bayes estimates, and third concentration was used for external validation. The plasma concentration at the time of the scan was predicted, and D₂ occupancy was then estimated by incorporating the predicted concentration[3].

Results: Observed and predicted D₂ occupancy levels were highly correlated (r=0.69, p<0.001 for olanzapine; r=0.65, p=0.02 for risperidone). In addition, the program optimized parameters and provided all relevant output in a matter of seconds. The user interface developed was convenient and simple to use for psychiatrists utilizing the program.

Discussion: The ability to predict dopamine receptor occupancy prior to a dose adjustment is clinically valuable due to the relationship between receptor occupancy and treatment outcomes. Use of the open source software, R programming, and published PK/PD models resulted in an accurate, and perhaps just as important for everyday use by clinicians, fast performing application.