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MONTE KARLO SIMULACIJA U FARMAKOKINETICI IMUNOSUPRESIVA

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Optimizacija imunosupresivne terapije kod pacijenata sa transplantiranim bubregom otežana je izraženom interindividualnom varijabilnošću u farmakokinetičkim procesima. Cilj ove studije bio je da se proceni primenljivost i izvrši validacija prethodno objavljenog populacionog farmakokinetičkog modela [1] mikofenolne kiseline (MPA) korišćenjem Monte Carlo (MC) simulacije, u cilju individualizacije doziranja i poboljšanja terapijskih ishoda.

MC numerička analiza sprovedena je kroz 1000 simulacija za svaki analizirani model, kako bi se dobio opseg očekivanih vrednosti klirensa MPA. Kliničke kovarijate su varirane u okviru opsega njihovih standardnih devijacija, a raspodela očekivanih vrednosti klirensa poređena je unutar samog modela i sa objavljenim modelima iz sličnih studija [2, 3]. MC analiza je izvršena korišćenjem softvera Matlab R2017b (MathWorks).

Simulacije su potvrdile robusnost našeg modela i identifikovale starost i koterapiju nifedipinom kao najuticajnije prediktore klirensa MPA. Primena nifedipina povećala je klirens za oko 18%, dok je stariji uzrast bio povezan sa povećanjem klirensa do 50% u analiziranom simulacionom opsegu. Poređenje sa spoljnim modelima pokazalo je dobro slaganje: u studijama gde je albumin bio značajna kovarijata, niže vrednosti albumina bile su povezane sa povećanjem klirensa za oko 15–25%, dok su drugi modeli naglašavali značaj kreatinina i telesne mase. Veći procenat slaganja između spoljnih i našeg modela zabeležen je kod pacijenata koji nisu koristili nifedipin, u odnosu na one sa koterapijom.

MC simulacija se pokazala kao dragocen alat za procenu farmakokinetičkih modela i identifikaciju ključnih prediktora varijabilnosti. Njena primena smanjuje potrebu za opsežnim uzorkovanjem i pruža podršku kliničkoj praksi u određivanju optimalne doze imunosupresiva, čime se potencijalno unapređuju bezbednost i efikasnost posttransplantacione farmakoterapije.

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MONTE CARLO SIMULATION IN IMMUNOSUPPRESSANT PHARMACOKINETICS

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The optimization of immunosuppressive therapy in kidney transplant recipients is challenged by pronounced interindividual pharmacokinetic variability. This study aimed to evaluate the applicability of a population pharmacokinetic model [1] of mycophenolic acid (MPA) using Monte Carlo (MC) simulation to support dose individualization and improve outcomes.

MC numerical analysis was performed with 1000 simulations per model to define the expected range of MPA clearance values. Clinical covariates were varied within their standard deviation ranges, and the distribution of predicted clearance was compared within the model and against published models from similar studies [2,3]. Analyses were conducted using Matlab R2017b (MathWorks).

The simulations confirmed the robustness of our model and identified age and nifedipine co-therapy as the most influential predictors of MPA clearance. Nifedipine co-administration increased clearance by approximately 18%, while advancing age was associated with a rise in clearance of up to 50% across the simulated range. Comparison with external models showed good concordance: in studies where albumin was a significant covariate, lower albumin levels were associated with an increase in clearance of about 15–25%, while other models emphasized the role of creatinine and body weight. A higher percentage of agreement was observed between external models and our model for patients not receiving nifedipine compared with those on concomitant therapy.

MC simulation proved to be a valuable tool for evaluating pharmacokinetic models and identifying key predictors of variability. Its application reduces the need for extensive sampling and supports clinical practice in determining the optimal dose of immunosuppressants, thereby potentially improving the safety and efficacy of post-transplant pharmacotherapy.

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