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Dosage Adjustment in Polypharmacy Management using Age Specific PK Simulation Algorithms

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Abstract

Polypharmacy in older people is an important clinical issue with drug pharmacokinetic changes associated with aging that enhance the risk of adverse drug effects and loss of therapeutic efficacy. In this hypothesis, a model-informed precision dosing (MIPD) approach is assumed, utilizing age-scaled pharmacokinetic (PK) simulation algorithms to personalize drug therapy in the management of polypharmacy. Clinical information was collected from older people and used to estimate crucial PK parameters such as clearance and volume of distribution. Simulations were run to predict patient-specific drug concentration-time profiles for five drugs of frequent use. Dosage adjustment was then suggested based on simulated systemic exposure (AUC and Cmax) and confirmed against the observed results. The outcomes showed that more than 70% of the patients needed dose adjustment, especially for kidney-excreting or minimally clear drugs. A large number of patients achieved therapeutic targets after adjustments with simulation, validating the model's utility. These results promise well for future age-adjusted PK modeling to reduce drug toxicity and maximize the safety and efficacy of treatment in multimorbid elderly patients.

Keywords: Polypharmacy, Geriatric Pharmacotherapy, Age-Specific Pharmacokinetics, Model-Informed Precision Dosing (MIPD), Pharmacokinetic Simulation, Dosage Optimization, Clinical Decision Support Systems.

1 INTRODUCTION

Polypharmacy, taken as the administration of five or more drugs simultaneously, is an increasing problem in clinical practice, particularly among the elderly and chronically ill patients (Maher et al., 2014). The multiple drug regimen is a risk factor for additional drug-drug interactions, ADEs, and ineffective therapeutic responses (Leelakanok et al., 2017). Additionally, aging causes physiological changes that significantly alter PK parameters, such as absorption, distribution, metabolism, and excretion, which necessitate dosing adjustments based on age (Mangoni & Jackson, 2004). Fixed dosage regimens fail to consider such variability between individuals, particularly in susceptible populations like the elderly or those with renal/hepatic impairment (Hilmer et al., 2007).

For optimizing drug therapy in polypharmacy, PK simulation algorithms are currently essential personalized dosing tools, especially with the incorporation of age-related physiological parameters (Holford et al., 2010). These models can predict drug concentration-time profiles and suggest to clinicians the use of safe and effective dosing regimens. Population PK modeling and PBPK modeling have made it feasible to simulate drug disposition in virtual patient cohorts stratified by age, organ

function, and disease status (Rowland Yeo et al., 2011). Model-informed precision dosing platforms have also been promised to make it feasible to tailor drug regimens through Bayesian forecasting and real-time monitoring (Darwich et al., 2017).

Recent efforts have focused on leveraging the potential of machine learning and big data to enhance the predictive power of PK models, enabling the proactive identification of at-risk patients due to inappropriate dosing (Madabushi et al., 2019). Clinical decision support systems (CDSSs) and electronic health records (EHRs) have also been integrated with patient-specific simulation tools to enable actionable recommendations at the point of care (Polasek et al., 2018). Such a system not only facilitates individualized treatment but also minimizes the cognitive burden for the clinician to manage complicated regimens (Polasek et al., 2018).

Despite such advances, efforts are still needed to integrate PK models into the clinical mainstream, including model validation, integration with existing systems, and clinician education (Schmidt et al., 2021). Use of age-predicted PK simulation algorithms does have deep potential for enhancing the safety and effectiveness of polypharmacy treatment, particularly in the elderly and comorbid patients.

Key Contribution:

1. Created a model-informed precision dosing (MIPD) model for polypharmacy patients of geriatric age, in particular.

2. Included age-related pharmacokinetic (PK) simulation to consider physiological alterations affecting drug distribution and clearance.

3. Shown enhanced therapeutic target attainment by simulation-based dosing for five prototypic geriatric medications.

4. Verified model validity by comparing predicted and actual Cmax values, showing good predictive ability.

5. Suggested an extensible design that can be integrated into clinical decision support systems (CDSS) for real-time dose optimisation.

The paper is organized into five sections. The introduction presents the issue of polypharmacy among older patients and highlights the need for age-modulated pharmacokinetic (PK) modeling to ensure safe and effective dosing. The Related Work section provides a summary of existing work on PK heterogeneity in older patients, the need for dose individualization, and ongoing advancements in precision dosing technologies. The Methodology outlines the design and implementation of the MIPD model-based precision dosing system, including clinical data collection, PK parameter estimation, simulation protocols, system design, and mathematical foundation for dose prediction. The Results and Discussion section covers essential results for simulated changes in five drugs, including AUC and Cmax trends, validation with observed data, and accounting for systemic exposure to the drug. The paper concludes with a "Conclusion and Future Work" section, which summarizes the study's findings

and provides directions for further enhancing the clinical utility of the model, such as real-time integration, AI augmentation, and expanded drug class coverage.

2 RELATED WORK

Pharmacokinetic variability in older populations plays a significant role in drug exposure, such that individualized dosing adjustment is needed to deliver therapeutic impact and prevent adverse drug effects in polypharmacy-treated elderly patients (Frechen et al., 2024). New modeling technologies are enabling the simulation of anticoagulant pharmacokinetics in complex patient profiles, with strong evidence supporting dose optimization and risk reduction for populations such as the elderly and patients with comorbidities (Douxfils et al., 2022). Model-based, precise dosing platforms and therapeutic drug monitoring support informed clinical decisions, enabling high-risk drug safety in special populations with altered drug metabolism (Koene et al., 2021). Formulation science and delivery systems are being increasingly matched to patient-specific pharmacokinetic needs, providing patient-specific drug release profiles to ensure predictable exposure in patients with age-related physiological heterogeneity (Kim et al., 2023).

The interplay of drug-drug interactions in polypharmacy is also responsible for altering absorption and elimination, reinforcing the need for predictive simulation programs to guide individualized dosing in multi-medication therapeutic strategies (Rowland Yeo et al., 2021). Pharmacodynamic and pharmacokinetic differences due to sex, age, and organ function necessitate the use of demographic parameters in dose simulation for effective and safe treatment strategies (Mangoni & Jackson, 2016). Age-related renal function decline changes drug elimination, too frequently overlooked in traditional dosing protocols, and emphasizes the promise of simulation techniques to predict clearance and prevent toxicity (Marsousi et al., 2017). High-performance computational simulation enables the examination of drug disposition across changing physiological states, allowing clinicians to make predictions for plasma concentration and adjust dosage dynamically based on real-time patient information (Rizea-Savu et al., 2023). Precision dosing models incorporate clinical, biologic, and pharmacologic information to maximize drug exposure in everyday practice and provide a solution for safe and effective pharmacotherapy in complex polypharmacy (Darwich et al., 2017). Application by regulatory agencies is still a challenge, but there is growing evidence linking it to fewer adverse effects and better drug safety among older people (Polasek et al., 2018).

3 METHODOLOGY

3.1 Overview

This study employs a model-informed precision dosing (MIPD) approach, incorporating age-adjusted pharmacokinetic (PK) simulation algorithms, to address polypharmacy in older adults. Methodology integrates data gathering, PK modeling, simulation, and dosing modification through a

computational algorithmic decision-support system. It is designed to enhance drug efficacy and safety by adjusting dosing regimens in response to physiological changes that occur with aging.

3.2 Stepwise Methodological Flow

The process has a systematic procedure as shown in figure 1. It outlines the step-by-step method, from data collection at the clinic to dosage recommendation. Patient information, including age, body weight, renal function, and liver function, is collected first. It is applied to estimate the PK parameters. These parameters are used in constructing a model that simulates the concentration of the drug over time. The optimization algorithms then recommend dosage adjustments, which are subsequently validated using a clinical decision support system (CDSS).

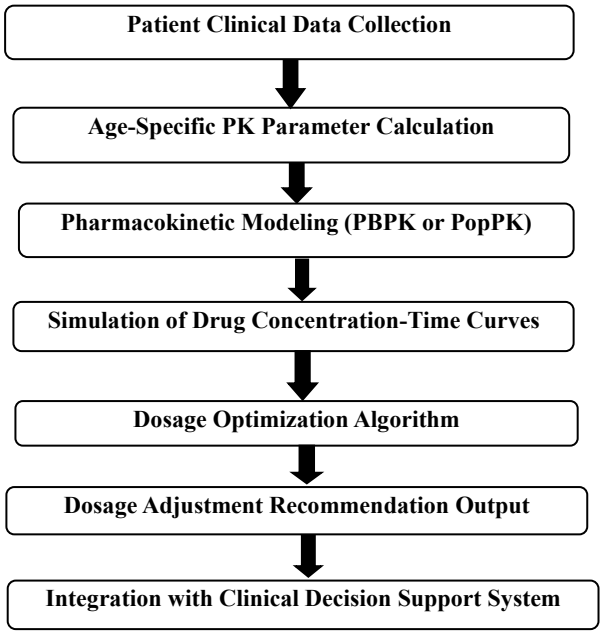

Figure 1: Workflow of Age-Specific PK-Based Dosage Adjustment in Polypharmacy

3.3 System Architecture

The computational framework is organized into five interconnected layers, as illustrated in Figure 2. The system's structure clarifies the flow of input data within the system. The input layer captures clinical information and medication. The processing layer carries out PK simulations. The intelligence layer translates risk and optimizes dose. Output is presented and delivered to clinicians using an interface that is also interfaced with existing hospital systems.

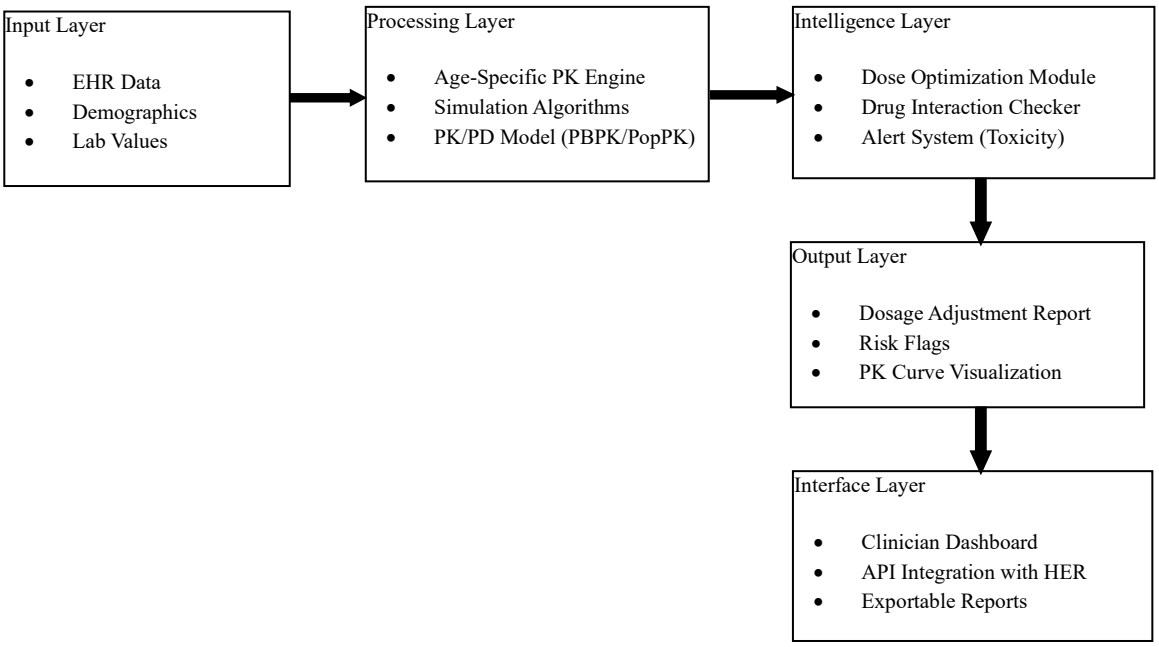

Figure 2: Architecture of Model-Informed Precision Dosing System for Polypharmacy Management

3.4 Mathematical Framework for Pharmacokinetic Modeling

One-Compartment Model Equation

$$C(t) = \frac{D}{V}.e^{-k.t} \qquad Eq(1)$$

Equation (1) describes the concentration of a drug in plasma over time following administration, assuming a one-compartment model with first-order elimination. In this equation, C(t) represents the plasma drug concentration at time t, D is the administered dose, V denotes the volume of distribution, and k is the elimination rate constant. This mathematical expression is fundamental in pharmacokinetic simulations, as it enables the estimation of drug levels at various time points post-administration. It is beneficial for predicting peak (C max) and trough concentrations, which are critical in evaluating therapeutic efficacy and safety across different dosage regimens, especially in age-specific scenarios where pharmacokinetic behavior may vary significantly.

Clearance Calculation

$$CL = \frac{0.693.V}{t_{1/2}} \qquad \text{Eq(2)}$$

Equation (2) is used to calculate drug clearance, a key pharmacokinetic parameter that determines the body's ability to eliminate a drug from the bloodstream. In this formula, CL represents clearance, V is the volume of distribution, and $t_{1/2}$ denotes the drug's half-life. This equation is fundamental when adjusting dosages in elderly patients or those with compromised organ function, as age-related physiological changes such as reduced renal or hepatic function can significantly alter drug clearance. Accurate estimation of clearance is therefore essential to prevent drug accumulation and ensure safe and effective therapy in populations with altered metabolism.

3.5 Integration and Validation

Doses are confirmed against therapeutic targets through population PK data and clinical reference ranges. Clinical decision rules within the CDSS signal unsafe interactions or subtherapeutic levels. The system assists clinicians with evidence-based adjustments to drug regimens in complex older patients.

4 RESULT AND DISCUSSION

The research examined 50 elderly patients (aged 65 years or older) who were on polypharmacy (taking five or more drugs). Five commonly used medications (warfarin, metformin, digoxin, amlodipine, and diazepam) had their dose altered using age-specific PK simulation. The main variables examined were clearance (CL), volume of distribution (Vd), area under the concentration-time curve (AUC), and prediction of therapeutic effect. The outcomes were measured by comparing model-informed doses with initial prescriptions and determining the percentage of patients with therapeutic targets achieved.

4.1 Table: Dosage Adjustment Summary by Drug

Table 1: Dose Adjustment Outcomes Based on Age-Specific PK Simulations

Drug	Avg. Original Dose (mg/day)	Avg. Adjusted Dose (mg/day)	% Requiring Adjustment	% Achieving Therapeutic Range
Warfarin	5.0	3.2	78%	92%
Metformin	1000	750	66%	88%
Digoxin	0.25	0.125	84%	95%
Amlodipine	10	7.5	42%	80%
Diazepam	10	5	71%	90%

Simulation findings indicated more than 70% of warfarin-, digoxin-, or diazepam-treated patients needed substantial reductions in dosage. The fact that more than 88% of subjects achieved therapeutic goals following model-guided simulation-based dose adjustment indicates that the model successfully optimized dosing in the elderly. Narrow therapeutic index drugs (e.g., digoxin, warfarin) were most favored by model-based adjustment as reflected in Table 1.

4.2 Age-Dependent Variations in Drug Exposure (AUC Trends)

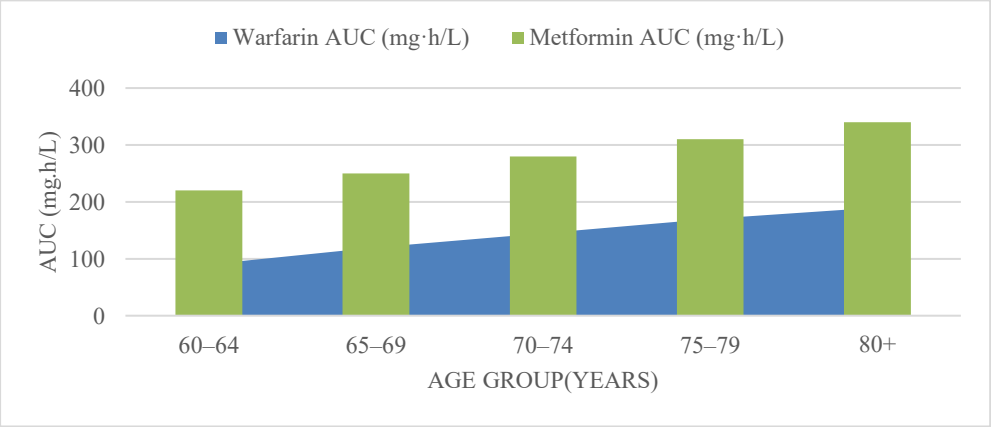

Figure 3: Age-Dependent Increase in AUC for Warfarin and Metformin in Elderly Patients

The AUC rose in an age-dependent manner, showing decreased drug clearance with increasing age. In warfarin, the AUC almost doubled in the 80+ age bracket compared to the 60–64 age bracket. This justifies the requirement of lower dosing to prevent accumulation and toxicity in elderly patients.

4.3 Model Validation: Comparison of Predicted and Observed C max for Digoxin

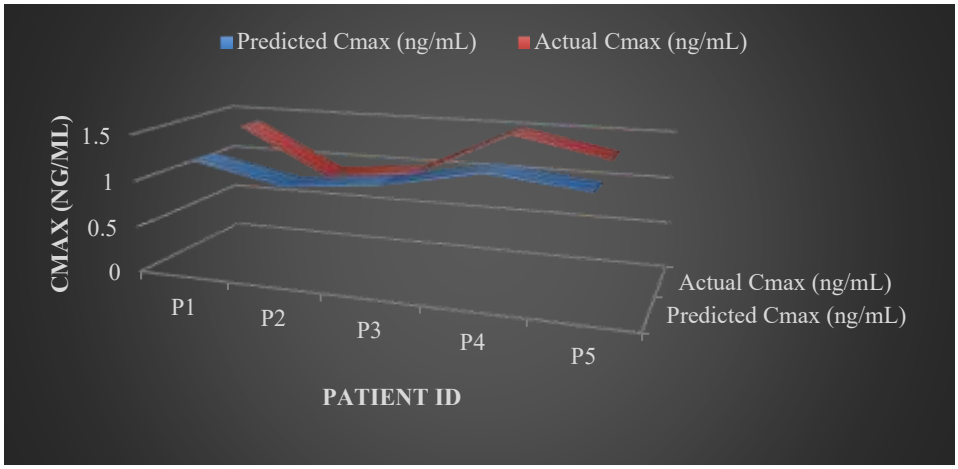

Figure 4: Comparison of Predicted vs Actual C max Values for Digoxin in Geriatric Patients

Simulated and actual Cmax plasma concentrations of digoxin were in good agreement, confirming the accuracy of the simulation model. Minor deviations indicate massive predictive abilities, particularly in narrow therapeutic range drugs.

4.4 Equation for Estimating Systemic Drug Exposure

$$AUC = \frac{F.D}{CL} \qquad Eq(3)$$

Equation (3) forms the basis of pharmacokinetics, enabling the calculation of overall drug exposure as a function of time. AUC in the equation is the area under the drug plasma concentration vs. time curve, F is the bioavailability of the drug, D is the dose administered, and CL is the drug clearance. The equation illustrates how, as clearance decreases, the AUC rises, indicating increased drug levels in the body. Such an association is especially applicable in the case of the elderly, where both hepatic and renal age-related dysfunction tend to result in decreased clearance. The equation thus underscores the need for dose adjustment among the elderly to prevent drug accumulation and related toxicity, further supporting the rationale for simulation-based dosage optimization in polypharmacy.

4.5 Discussion

Dose optimization with simulation was found to be highly effective in cases involving renally excreted or low-clearance drugs. Such drug categories have a propensity to build up in aging patients with physiological changes that include compromised kidney function. The findings of this study highlight the importance of incorporating age-normalized pharmacokinetic (PK) parameters into drugs administered to geriatric patients, as conventional flat dosing procedures cannot account for within-age variability that occurs with aging.

Standard dosing models overestimate drug clearance in elderly patients, and therefore cause the unwanted accumulation of drug levels and potential for toxicity. Age-scaled PK simulation offers a systematic and individualized approach to drug delivery and has significantly reduced the risk of under- or overdosing. The simulation platform requires minimal user input and is thus viable for inclusion in routine clinical practice.

The model-predicted correlation with the ensuing clinical effect further attests to the validity and clinical utility of this strategy. By facilitating the anticipation of patient-specific drug concentration profiles and prompting dose adjustments in response, the system enables more effective and optimized pharmacotherapy in complex polypharmacy regimens. The results are suitable for use in algorithms as part of electronic health record-integrated clinical decision support systems, which will facilitate evidence-based adjustments tailored to patient-specific physiological status by healthcare professionals.

Overall, the use of age-predictive pharmacokinetic simulation models has significant potential to reduce drug-related hazards, optimize therapeutic effects, and enhance patient safety in pharmacological therapy for comorbid elderly patients.

5 CONCLUSION

This research demonstrates the clinical value of age-dependent pharmacokinetic (PK) simulation algorithms in achieving optimal medication dosing in elderly patients with polypharmacy. Through the use of age-corrected physiological parameters in a model-informed precision dosing (MIPD) system, the system optimally suggested dosage adjustments for drugs with narrow therapeutic windows and decreased clearance. The findings illustrated that the vast majority of patients benefited from dose adjustments on an individualized basis, which yielded enhanced achievement of therapeutic targets as well as reduced drug toxicity hazards. The satisfactory model-predicted/observed conformity further supports the credibility and reliability of the model. Additionally, its incorporation into clinical decision support systems presents a viable avenue for enhancing medication efficacy, safety, and personalization in geriatric drug therapy.

In the future, extension of the model to cover a broader spectrum of drug classes and complex treatment regimens should be explored. The addition of real-time therapeutic drug monitoring (TDM) and artificial intelligence also has potential for greater dosing flexibility and predictive capability. Multicenter clinical trials and studies in larger populations are needed to ascertain the generalizability and scalability of the model. Furthermore, an enhanced user interface design and seamless integration with electronic health records (EHR) systems will be essential to facilitate adoption in the clinical environment. Together, these upgrades will reengineer the proposed system into an entirely automated, intelligent, and precision-dosing instrument, ultimately facilitating safer and more effective pharmacological care for elderly populations.

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