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Requires Data Access? Yes

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Requires Data Access? Yes

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: We receive financial support from university.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2023/12/ziqiwang-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2023/12/luyaohan-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2023/12/guoyu-COI.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT01998971 - An Open-Label, Multicenter, Phase 1b Study of JNJ-54767414 (HuMax CD38) (Anti-CD38 Monoclonal Antibody) in Combination With Backbone Regimens for the Treatment of Subjects With Multiple Myeloma
2. 97-024 - Multiple-Dose Pharmacokinetic Study of an Ibuprofen-Psuedoephedrine HCl Suspension in Children. Aug 1999.

3. NCT00821600 - Single-Dose, Open-Label Pilot Study to Explore the Pharmacokinetics, Safety and Tolerability of a Gluteal Intramuscular Injection of a 4-Week Long-Acting Injectable Formulation of Risperidone in Patients With Chronic Stable Schizophrenia
4. NCT01559272 - A Single-Dose, Open-Label, Randomized, Parallel-Group Study to Assess the Pharmacokinetics, Safety, and Tolerability of a Paliperidone Palmitate 3-Month Formulation in Subjects With Schizophrenia
5. NCT01876966 - A Phase I, Partially Randomized, Open Label, Two-way, Two Period Cross-over Study to Investigate the Pharmacokinetic Interaction Between Etravirine or Darunavir/Rtv and Artemether/Lumefantrine at Steady-state in Healthy HIV-negative Subjects
6. NCT02195869 - A Multicenter Open-Label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease
7. NCT03359291 - A Single-center, Open-label, One-sequence, Two-treatment Study to Investigate the Effect of Macitentan at Steady State on the Pharmacokinetics of Rosuvastatin in Healthy Male Subjects.
8. Tolerability and Multiple-Dose Pharmacokinetics of Acetaminophen (Paracetamol) At and Above the Currently Recommended Maximum Daily Dose

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Development of a model to simulate the pharmacokinetics of drugs in patients with different characteristics to advance precision medicine

Narrative Summary:

Our team has built a model framework using acquired human blood drug concentration with the combination of artificial intelligence and models of pharmacometrics. In order to ensure the accuracy and generalization of the model, quantities of individual parameters and clinical data were desired to train the model, thus representing the real differences of populations and individuals. Our current purpose is to establish a virtual human model covering adults and children by reinforcement learning, which can simulate the interaction between drugs and populations according to the real drug exposure and individual physiological environment, to promote the process of precision medicine.

Scientific Abstract:

Background□myeloma is a cancer of white blood cells that attacks and destroys bone. In the development of pharmacokinetics (PK), model-informed drug development (MIDD) has been an auxiliary mean of the mainstream to guide drug research and decision-making by utilizing pre-clinical and clinical exposure data, biological and statistical models.
Objective; Our current purpose is to establish a virtual human model covering adults and children by reinforcement learning, which can simulate the interaction between drugs and populations according to the real drug exposure and individual physiological environment, to promote the process of precision medicine.
Study Design: Combining artificial intelligence with pharmacological model, reinforcement learning method is used to build a model framework based on the obtained human blood drug concentration. In order to ensure the accuracy and generalization ability of the model, a large number of individual parameters and clinical data are needed to train the model, so as to reflect the real differences of the population and individuals.
Participants; Patients of all ages and races with myeloma .

Primary and Secondary Outcome Measure(s): the maximum tolerated dose (MTD) and PK profiles.
Statistical Analysis:The blood drug concentration data, demographic and clinical characteristics of human were processed by deep learning.

Brief Project Background and Statement of Project Significance:

In the development of pharmacokinetics (PK), model-informed drug development (MIDD) has been an auxiliary mean of the mainstream to guide drug research and decision-making by utilizing pre-clinical and clinical exposure data, biological and statistical models, which mainly includes PBPK model and popPK model. Both FDA and NMPA have issued corresponding guiding principles related to MIDD.
Composed of numerous differential equations, traditional PBPK models simulate the process of in-vivo drug circulation following large composite error. Plenty of drug parameters and physiological parameters need to be gathered during the model-building process due to its bottom-up mechanistic characteristic. Despite the fact that most of the currently available commercial software has typical physiological parameters embedded, it is difficult to carry out individualized simulation in batches, and usually only the average predicted value can be obtained. The majority of currently available commercial software has embedded with typical physiological parameters of population, rendering it frequently simply yielding the average anticipated value and challenging to perform personalised simulation in batches.
PopPK models generalize the mapping relationship of nonlinear mixed model following a “top-down” mode by machine learning, remaining to be relatively rough and sweeping.
Despite the considerable achievements made in PK fields by the current model methodologies, the cost of clinical trials has not been greatly reduced. With the outbreak of new artificial intelligence (AI) technology, its application for drug research and development has now entered a period of rapid growth. AI technology is mainly focused on the stage of drug discovery, including prediction of disease targets and signal pathways, high-throughput quantitative structure-activity relationship (QSAR), and absorption, distribution, metabolism, excretion and toxic (ADMET) screening of lead compounds, etc.
n our research, AI is expected to be combined with the present pharmacometric models and theories and applied to clinical trials to reduce the failure rate or the costs, assisting the process of new drug research and development.

Specific Aims of the Project:

In our research, AI is expected to be combined with the present pharmacometric models and theories and applied to clinical trials to reduce the failure rate or the costs, assisting the process of new drug research and development.
Reinforcement learning is an important branch of AI, especially suitable for solving the problem of multi-round games or sequential decision-making. The environment in reinforcement learning is not in the usual sense, but dynamic with specific behavior and state transformation. AlphaGo Zero is one of the classic application scenarios of deep reinforcement learning. It only uses deep reinforcement learning, and the achievements of three-day zero-start training have far exceeded the knowledge accumulated by human beings for thousands of years, without any human historical chess manual. The pharmacokinetic scenarios can be described in almost the same way. The interaction between human body and drugs is a dynamic environment which is finally presented as the dynamic plasma concentration in PK.
At present, our team has built a model framework using acquired human blood drug concentration. However, it is prone to over-fitting and poor generalization owning to the limitation of clinical data. In order to ensure the accuracy and generalization of the model, quantities of individual parameters and PK data were desired to train the model, thus representing the real differences of populations and individuals.
Our research was designed to construct high-fidelity in silico human models—VirtualBody, that can authentically mirror the multifaceted and individualized effects of drugs on human. Integrating physiological priors, empirical data, and drug properties, VirtualBody demonstrates robust predictive performance on individuals not encountered during training, effectively capturing intricate physiological processes. It is feasible to use different kinds of trials with pharmacokinetic results for our human models because our models are not pharmacodynamic oriented. So these eight different

kinds of trials were applied, and the pharmacokinetic data of different drugs in these trials were applied to the models in the hope of demonstrating that the model has a relatively good predictive performance on different kinds of drugs and patients with different physiological characteristics.
In conclusion, our purpose is to establish a virtual human model by reinforcement learning that can simulate the interaction between drugs and human body according to the real drug exposure and individual physiological environment, narrowing the gap between drug clinical development and drug application.

Study Design:

Other

Study Design Explanation:

Training with clinical data

What is the purpose of the analysis being proposed? Please select all that apply.

Develop or refine statistical methods

Research on clinical prediction or risk prediction

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Eligible patients were those with myeloma and have not received any prior therapy for myeloma and WHO presentation status of 2 or lower.
There was no limit to ages and races.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The primary outcome is to build the Algorithm for predicting pharmacokinetics in individuals.No secondary outcome measure.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Main Predictor is PK profiles in individuals(plasma concentration)
We collect the individual characteristics of patients, information about drug administration to categorize .eg:
Patient Demographic Information:Age□Gender□Height□Weight□Ethnicity□Geographic □location
Lesion Information:Lesion site (e.g., lung, liver, brain)□Lesion size□Lesion shape□Lesion density or intensity
Pathological Information:Pathological type (e.g., cancer, inflammation)□Pathological grade or stage□Whether it has metastasized or not
Pre-surgical Information:Pre-surgical symptoms and signs□Pre-surgical laboratory test results□Pre-surgical imaging findings (e.g., X-ray, CT, MRI)□
Treatment Plan Information:Surgical approach (e.g., open surgery, minimally invasive surgery)□Chemotherapy plan□Radiation therapy plan□Other treatment options (e.g., medication, immunotherapy)
Post-surgical Information:Post-surgical symptoms and signs changes□Post-surgical laboratory and imaging findings changes□Post-surgical complications□Post-surgical recovery progress□Post-surgical quality of life assessment

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

We define biochemical indicators as variable if applicable, which were linked to the pharmacokinetic (PK) parameters of the drug.

Statistical Analysis Plan:

Reinforcement learning is an important branch of AI, especially suitable for solving the problem of multi-round games or sequential decision-making. The interaction between human body and drugs is a dynamic environment which is finally presented as the dynamic plasma concentration in PK. At present, our team has built a model framework using acquired human blood drug concentration. However, it is prone to over-fitting and poor generalization owning to the limitation of clinical data. In order to ensure the accuracy and generalization of the model, quantities of individual parameters and PK data were desired to train the model, thus representing the real differences of populations and individuals.
The population data and drug PK data will be uniformly cleaned up according to the required variables. Specifically，VirtualBody models the transition of PK as a Markov Decision Process (MDP), defined by a tuple M = (S, A, M∗, r, γ, ρ0) ，where S is the state space, A is the action space, and M∗ is the optimal (i.e., real-world) transition model. As for our MDP, it mainly consisted of three key elements:
(1) States incorporated detailed information about the drug, including its chemical properties and patient-specific features derived from the HAD Model. Time information is also included to ensure the Markov property is
satisfied. In addition to the time-independent features, the dynamic drug concentration transition data is an essential dimension for the states, as our model is optimized to generate drug concentration-time curve.
(2) Actions at a given time step were two-dimensional, with the first dimension being the medicine dosage and the second dimension representing patients' diets.
(3) State transitions defined the probability distribution over the next states, i.e. the PK data at the next time point, given a state and an action.
The learning objective of VirtualBody was to predict the subsequent state for each time step within the trajectory in this MDP, based on the corresponding state-action pair at that particular step.
The required variables will be incorporated into the model, so that the agent can understand the characteristics of various types of drugs and learn the rules.
For the missing data value, we will take a population average to supplement it.

Software Used:

Python

Project Timeline:

anticipated project start date：2023.12
analysis completion date：2024.8
date manuscript drafted ：2024.10
first submitted for publication：2024.11
and date results reported back to the YODA Project: 2025.1

Dissemination Plan:

Anticipated Products and Target Audience Description：
This project on blood drug concentration prediction aims to develop a tool that can accurately predict individual blood drug concentrations. This tool can provide personalized advice to medical teams, pharmacists, and patients on drug dosages and administration times,□□□□ drug efficacy and reducing side effects.
Target Audience：
The target audience includes medical professionals such as doctors and pharmacists, as well as

patients who require long-term drug therapy.
Anticipated Research Manuscripts and Potentially Suitable Journals for Submission of the Completed Research Project
Upon completion of the project, it is expected that multiple research manuscripts will be produced, detailing the development process, validation results, and comparisons with other prediction models. These manuscripts will focus on the accuracy of drug concentration predictions, the ease of use of the tool, and its application in clinical practice.
For the submission of these research manuscripts, journals with high impact factors in the fields of clinical pharmacy or drug therapy, such as " Clin Pharmacol" , are expected to be selected. These journals have a wide influence in the pharmacy and medical fields, which will help promote the application and dissemination of the project's results.

Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2023/12/2023-5502-Addendum.pdf