



Overview of Korean Pharmacometrics Modeling Library and web-based pharmacometrics platform

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Background and Objective

As an increasing number of pharmacometrics (PM) models have been developed based on data in Korea, which leads to the needs of archiving and further using developed models. In addition, a growing demand for prediction pharmacokinetic (PK) parameters in an easy way leads to motivation of developing an easy-to-use platform where one can easily estimate PK parameters in diverse methods. As those of trends, Korean Pharmacometrics Model Library (KPML) has been developed by collaboration of Ministry of Food and Drug Safety (MFDS) and Korean Society for Clinical Pharmacology and Therapeutics (KSCPT) as a web repository and platform to store the developed PM models in Korea and provides PM platform for estimate PK parameters using various methods such as non-compartment (NCA), compartment model (CA), allometric scaling (AS), or *in vitro in vivo* extrapolation (IVIVE).

Methods

- KPML**
 - Collect and store model code and dataset pharmacometrics models in Korea (including of PK model, PKPD model, PBPK-PD model)
- PM platform**
 - NCA: Develop based on some R packages, including bear (v2.8.7) [1], NonCompart (v0.4.5), and ncar (v0.4.2) [2]
 - CA: Develop using nlmixr package in R [3]
 - AS: Develop in R to extrapolate PK parameters from animal to human using single species scaling or simple allometric scaling equations
 - IVIVE: Develop in R to estimate *in vivo* hepatic clearance (CL_h) from *in vitro* CL_h using three different methods (well-stirred, parallel and dispersion method)
- PM training**
 - Provide materials related to PM works (lecture files, hands-on, including code files and data files, and result files)
- Guidelines**
 - Update PM guideline from FDA, EMA, MFDS, ICH and other sources

Results

- KPML provide developed models where one can refer when developing models for drugs

Table. Number of current available models in KPML

| Type of model | PK model | PK-PD model | PBPK-PD model |
|------------------|----------|-------------|---------------|
| Number of models | 15 | 4 | 5 |

One compartment PK model of Vancomycin

| Item | Details |
|--|---|
| Model name | One compartment PK model of Vancomycin |
| Author name | Hyun-moon Back |
| Reference | None |
| Drug | Vancomycin |
| Target Disease | MRSA infection |
| Objective | Development of vancomycin pharmacokinetic model in pediatric patients |
| Description | One compartment PK model with I.V. infusion in pediatric patients |
| Matching model and Reference | true |
| Modification with Respect to publish model | true |
| Modeling Dataset | human |
| Data Description | Pediatric patients |
| files | run20.lst run20.mod Vanco_PK_data_LNDV_Final.csv |

Code, dataset and result file

- PM platform provide environment where one can upload data and calculate PK parameters

Non-Compartmental Analysis/Compartmental Modeling

Available Graphs: Individual Time vs. Concentration, Time vs. Concentration, Spaghetti plot of Time vs. Concentration, Box Whiskers Plot.

In vitro In vivo Extrapolation

Input Data: v_{max} (nmol/min/mg), K_m (μmol/L), f_p , f_{m1c} , Q_h (mL/min/kg), D_h , Hepatocyte number (cells/g Liver), Liver weight (g Liver/kg Body weight).

Result (mL/min/kg): Well-stirred, Parallel, Dispersion.

Allometric scaling

Choose species: (human)

Drug name:

Net clearance (mL/min/kg):

Net volume of distribution (L/kg):

Net clearance in human (mL/min/kg):

Net volume of distribution in human (L/kg):

Estimate PK parameters in human

CL (mL/min/kg), Vd (L/kg), Half-life (h)

- PM training provide materials where one use it to learn and practice

| Model Name | Author Name | Drug | Target Disease | Modeling Dataset | Data Description | Model ID |
|--|------------------|------|----------------|------------------|------------------|----------|
| Building Dataset & Writing Control Stream | In-hwan Baek | - | - | human | - | 179 |
| Structural Model Building and Evaluation | Eun Kyoung Chung | - | - | human | - | 180 |
| Covariate model building-1 | Jung-woo Chae | - | - | human | - | 181 |
| Covariate model building-2 | Hyun-moon Back | - | - | human | - | 182 |
| Model-based Simulation for Pediatric Dose optimization | Nayoung Han | - | - | human | - | 183 |
| NLME_Population PK models | - | - | - | human | - | 184 |
| NLME_Covariate effects | - | - | - | human | - | 185 |
| NLME_Categorical response | - | - | - | human | - | 186 |
| NLME_Allometric scaling | - | - | - | human | - | 187 |

- Guidelines provide update guidelines where one can easily find needed information

| Model Name | Author Name | Drug | Target Disease | Modeling Dataset | Data Description | Model ID |
|--|-------------|------|----------------|------------------|------------------|----------|
| Exposure-Response Relationships - Study design, Data analysis, and Regulatory Applications | FDA | - | - | human | - | 210 |
| Population Pharmacokinetics | FDA | - | - | human | - | 211 |
| Physiologically Based Pharmacokinetic Analyses - Format and Content | FDA | - | - | human | - | 212 |
| Integrated Summary of Effectiveness | FDA | - | - | human | - | 213 |

Conclusion

KPML with updated PM models is a precious repository which can be referred for developing new models or used in clinical practice. In addition, KPML with potential platforms would be an easy tool to predict precisely and reliably PK parameters. It can be widely applied to quickly predict and reduce time and unnecessary effort on prediction PK parameters.

Reference

- [1] "The data analysis tool for average bioequivalence (ABE) and bioavailability (BA)." Available: <http://pkpd.kmu.edu.tw/bear/>.
- [2] Kim et al. Translational and Clinical Pharmacology. 2018, 26(1), 10-15.
- [3] Schoemaker et al. CPT Pharmacometrics Systems Pharmacology. 2019, 8(12), 923-930.



Available link website: <http://repository.kscpt.org/>

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