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Individual Control Optimization of Drug Dosage Using Individual Bayesian Pharmacokinetics Model Approach

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Abstract

Giving the right dose of medicine is very important in the healing process from a disease. Improper dosing may worsen the disease or even can cause death. Drug dosing should not only be done based on the population because each individual has different body characteristics. Therefore, the drug dosage was carried out individually using the individual Bayesian pharmacokinetics modeling approach. This case evokes problems regarding how to obtain the estimated population and individual parameters and then determine the optimal dose. The purpose of this analysis is to get the parameters estimation of both population and individual and determine their optimal dose. The data used in this study is patient data who received gentamicin injection. Variables used is gentamicin levels in serum as response variables and sampling times and initial doses as predictor variables. The results obtained are individual pharmacokinetic models with 100% prediction accuracy and dose ranges that can still be tolerated for each individual.

Keywords: Bayesian; Dosage; Pharmacokinetics; Gentamicin

1. Introduction

The drug is an important component in health because the drug is needed in the process of prevention, recovery, and treatment against an illness. The drug, however, can also cause adverse effects on health when the usage is improper. Improvement of the dosing system is an attempt to prevent mistakes in dosing the drug to patients in the

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future [1]. A field of science that has been developed to overcome this problem is pharmacokinetics. This method is studying drug movement in the human body, starting from the process of absorption, distribution, metabolism, and excretion (ADME). ADME process in the body could be described as a mathematics relationship in the form of changes in concentration based on time in system inspected, called pharmacokinetic models. The process description could be in the form of one model compartment and two model compartments.

Drug dosing should not only be done by dosing the population but also individually. This is done because each individual has a different characteristic viewed from factors that affect pharmacokinetics such as body weight, age and body surface area. Different pharmacokinetics characteristic in each individual allows different dosages to be received by each individual. Several studies have been developed to estimate the value of pharmacokinetic parameters, both in population and individual pharmacokinetic modeling. The studies that have been conducted on pharmacokinetics include [2] which compared and validated three models of population pharmacokinetics flucytosine (5-FC) using Standard Two-Stage (STS), Nonparametric Expectation Maximization (NPEM) and Nonlinear Mixed Effect Modeling (NONMEM). The pharmacokinetic model analyzed was an open compartment model. The results of the analysis stated that NONMEM is the most reliable and accurate pharmacokinetic model for the case of the flucytosine (5-FC) population. [3] conducted a study stating that the NPAG algorithm applied pharmacokinetic parameters iteration faster compared to the NPEM algorithm. Another study conducted by [4] to build its goal to developed Bayesian estimators Maximum A Posteriori (MAP) on the pharmacokinetics of mycophenolic acid is capable of accurately estimating inter mycophenolic acid AUC dose in patients with kidney transplants using blood samples. The analysis carried out stated that the MAP-Bayesian estimator of mycophenolic acid systemic exposure in different post-transplantation periods can be designed for the first time. [5] modeling individual pharmacokinetics in patients receiving injections gentamicin by the population with NPEM and individuals with MAP, which in turn result in improved individual dose. Furthermore, [1] also analyzed with the same data, but what is done is to make the NPAG algorithm program with Matlab. [6] also did the same thing with [5], but the data used was amikacin and compared the parameters of drug elimination rate (K) Vs volume of distribution (V) with slop of K for kidney function, creatinine clearance (Ks) Vs V, where pharmacokinetics using the K Vs V parameter is better than Ks Vs V.

This study is intended to do dosing to urological surgery for patients who receive an injection of gentamicin individually using Bayesian Pharmacokinetic Using Gibbs Sampler (PKBUGS) to estimate population pharmacokinetic parameters where the pharmacokinetic parameters obtained from the population will be used to estimate individual parameters using Maximum A Posteriori (MAP). The expected results of this study are how to obtain the appropriate pharmacokinetic parameters of the population and individuals in the case of gentamicin administration to urological surgery patients while obtaining the optimal dosage. This research is almost the same as the research conducted by [5], but there are differences in the stages of modeling population pharmacokinetic parameters that place more emphasis on Bayesian analysis. Furthermore, the result parameters from individual assessments will be used for individual dosing.

2. Literature

2.1. Pharmacokinetics

Pharmacokinetics study drug movement drug in the human body starting from the process of absorption, distribution, metabolism, and excretion (abbreviated with ADME) [7]. The pharmacokinetic model can provide a more rigorous interpretation of the relationship between drug levels in plasma and pharmacological responses. The simplest pharmacokinetics model is one compartment model. The pharmacokinetic model one compartment is:

$$y = \frac{D}{V} e^{-kt} \tag{1}$$

with

$$k = \frac{Cl}{V} \tag{2}$$

where y is the drug concentration at time t, V is the volume of distribution, Cl is the clearance, k is the elimination rate constant and t is the time for administering a certain dose of the drug.

In pharmacokinetics, individual dosing can be calculated by the following equation

$$\hat{D}_i = \frac{\hat{y}_{ij}\hat{V}_i}{\exp\left(-\hat{k}_i t_{ij}\right)} \tag{3}$$

where $\hat{D}_i$ is an ith individual dose estimation, $\hat{y}_{ij}$ is the peak concentration of the drug on the ith individual on jth observation, $\hat{V}_i$ is the volume of distribution on the ith individual $\hat{k}$, is the elimination rate on ith individual and tij is the peak time of the drug on the ith individual at the jth observation.

2.2. Population pharmacokinetic modelling

The Bayesian model developed from the Bayes method. The basis of this method is Bayes theorem. The prior distribution is part of important Bayesian inference and represents information about uncertain parameters which combined with new data probability distribution to produce posterior distribution which is used for the conclusion and future decision future which involving prior distribution. The main problems in set entered into prior distribution and distribution posterior character produced. In terms of the large sample size and parameter identified, a reasonable choice from previous distribution will have small effect small on posterior conclusion [8].

In Bayes theorem, there is prior information update using sample information contained in data through the likelihood function which is written as the following

$$p(\boldsymbol{\theta} \mid x) = \frac{L(x \mid \boldsymbol{\theta})\, p(\boldsymbol{\theta})}{p(x)} \tag{4}$$

which $\boldsymbol{\theta} = (\sigma, V, Cl)$, $p(\boldsymbol{\theta} \mid x)$ is posterior distribution, $p(\boldsymbol{\theta})$ is prior distribution, $L(x \mid \boldsymbol{\theta})$ is likelihood value from the sample and $p(x)$ is normalized constant which can be ignored [5] so that posterior distribution can be written

$$p(\boldsymbol{\theta} \mid x) \propto L(x \mid \boldsymbol{\theta})\, p(\boldsymbol{\theta}). \tag{5}$$

One of the modeling techniques used in the case of pharmacokinetics is the Markov Chain Monte Carlo (MCMC) technique. One of the most important and well-known MCMC methods is Gibbs Sampler. Gibbs Sampler has based on the characteristic that a multivariate distribution is unique which is determined by a conditional distribution. For pharmacokinetic cases, it means $\boldsymbol{\theta} = (\sigma, V, Cl)$ so the posterior form of the joint is $p(\sigma, V, Cl \mid y)$. Gibbs Sampler will help estimate parameters σ, V Cl and iteratively by following the sampling scheme as follows.

1. Sample $\sigma^{(k+1)}$ from $p\left(\sigma \mid V^{(k)}, Cl^{(k)}, \boldsymbol{y}\right)$.
2. Sample $V^{(k+1)}$ from $p\left(V \mid \sigma^{(k+1)}, Cl^{(k)}, \boldsymbol{y}\right)$.
3. Sample $Cl^{(k+1)}$ from $p\left(Cl \mid \sigma^{(k+1)}, Cl^{(k)}, \boldsymbol{y}\right)$.

Where $p\left(\sigma \mid V^{(k)}, Cl^{(k)}, y\right)$, $p\left(V \mid \sigma^{(k+1)}, Cl^{(k)}, y\right)$ and $p\left(Cl \mid \sigma^{(k+1)}, Cl^{(k)}, y\right)$ is posterior marginal for σ, V and Cl. Thus Markov chain is obtained which means $\boldsymbol{\theta}^{(k)}, \boldsymbol{\theta}^{(k+1)}$ $\boldsymbol{\theta}^{(k-1)}, \boldsymbol{\theta}^{(k-2)}, \ldots$ not interrelated. It is proven that samples from the posterior distribution achieved by following the Gibbs Sampler scheme. However, it might take a long time

for convergence and sample algorithms from the posterior distribution, therefore the initial part of the chain must be removed.

In the case of pharmacokinetics, if only drug concentration in plasma is observed in individuals i $(i = 1,...,K)$, the concentration of drug in the body to k^{th} observations of individual i (y_{ij}) and related to the time of observation (t_{ij}). Vector pharmacokinetic parameters for individuals i denoted by $\boldsymbol{\theta}_i$ with size $p \times 1$ or $\boldsymbol{\theta}_i = (\theta_1, \theta_2, ..., \theta_p)^T$. In the first stage of the hierarchy model, the form of opportunity distribution of each y_{ij} in the form of $\boldsymbol{\theta}_i$ and τ certain like

$$p(y_{ij} \mid \boldsymbol{\theta}_i, \tau) \sim N(f_{ij}, \tau^{-1} v_{ij}), \text{ for } \begin{matrix} i = 1,...,K \\ j = 1,...,n_i \end{matrix} \tag{6}$$

with $y_{ij} \sim N(f_{ij}, \tau^{-1} v_{ij})$, conditional $\underset{\sim}{\theta_i}$ and τ (distance between dosages), f_{ij} is a pharmacokinetic model that has been evaluated on t_{ij} with individual pharmacokinetic parameters equal to $\underset{\sim}{\theta_i}$, that is $f(\boldsymbol{\theta}_{ij}, t_{ij})$ and v_{ij} is the structure of the residual error. Note that other distributions other than normal distribution may be selected, such as lognormal or *t*-student distribution.

On the second stage hierarchy model, the distribution assumption is as follows.

$$p(\theta_i \mid \boldsymbol{\mu}, \boldsymbol{\Omega}^{-1}) \sim N_p(\boldsymbol{\mu}, \boldsymbol{\Phi}), \text{ for } i = 1,...,K \tag{7}$$

with N_p is a normal multivariate distribution $\boldsymbol{\mu}(p \times 1)$ is pharmacokinetics population behavior $\boldsymbol{\Omega}_{(p \times p)}$ is variance-covariance matrix representing an ISV (Interstudy Ability).

In the third stage, the hierarchy model can be shown by setting prior density for parameters $\tau, \boldsymbol{\mu}$ dan $\boldsymbol{\Omega}$.

$$p(\tau) = G(\alpha, \beta), \tag{8}$$

$$p(\boldsymbol{\mu}) = N_p(\boldsymbol{\eta}, \boldsymbol{c}) \tag{9}$$

$$p(\boldsymbol{\Omega}^{-1}) = W_p\left(\boldsymbol{R}^{-1}, \rho\right) \tag{10}$$

with $G(\alpha, \beta)$ is a gamma distribution with parameters α β and, $\boldsymbol{\eta}(p \times 1)$ is a μ prior estimation with covariant-variant matrix $\boldsymbol{c}$ and W_p shows a p-dimension of Wishart distribution with an average $\boldsymbol{R}^{-1}(p \times p)$ and free degree ρ [9].

From the third stage, iterations will be carried until converged. In this case, the expected value to be converged is $\boldsymbol{\mu}$. This is done because the value $\boldsymbol{\mu}$ will be used to determine pharmacokinetic parameters. The results of the estimation of pharmacokinetic population parameters are exponential values $\boldsymbol{\mu}$, with $V = \exp(\mu_2)$ a while $Cl = \exp(\mu_1)$.

2.3. Pharmacokinetics modeling individual i^{th}

The analysis method used for the drug dose individualization is the Maximum A Posteriori (MAP). In each individual, individual parameters are obtained by minimizing the following objective functions:

$$MAP = \sum_{i=1}^{U} \frac{\left(y_{ij} - \hat{f}(\hat{\underset{\sim}{\theta}}_i, t_{ij})\right)}{\hat{s}_d^2(y_{ij})} + \frac{\left(\overline{V} - \hat{V}_i\right)^2}{\hat{s}_d^2(V)} + \frac{\left(\overline{k} - \hat{k}_i\right)^2}{\hat{s}_d^2(k)} \tag{11}$$

where

U = number of drug concentration measurement on the i^{th} individual

y_{ij} = individual drug concentration data on the i^{th} individual at the j^{th} observation

$\hat{f}(\hat{\theta}_i, t_{ij})$ = pharmacokinetic predictive models on individual i^{th}, which has been evaluated at t_{ij}

$\overline{V}$ = volume of population distribution

$\overline{k}$ = rate of population elimination

$\hat{V}$ = predictive value of the volume of distribution on i^{th} individual

$\hat{k}_i$ = prediction of the value of the elimination rate in the i^{th} individual

$\hat{s}_d(y_{ij})$ = deviation standard of drug concentration in the i^{th} population

$\hat{s}_d(V)$ = standard deviation of the volume of distribution of the i^{th} population

$\hat{s}_d(k)$ = standard deviation of the i^{th} population elimination rate

Function $\hat{s}_d(y_{ij})$ estimated using a second order regression model that stated the drug concentration observed in serum. The function can be written as

$$\hat{s}_d(y_{ij}) = \hat{\beta}_0 + \hat{\beta}_1 y_{ij} + \hat{\beta}_1 y_{ij}^2 \tag{12}$$

The function is a laboratory deviation pattern, where measurements of each level are carried out in the laboratory with repetition.

The process of MAP optimization is done by the Nelder-Mead Simplex iteration, namely by replacing the worst settlement point with the best.

3. Methodology

The data used in this research is secondary data taken from [10]. The subjects studied were 13 urological surgery patients at Syaiful Anwar Malang Hospital who received gentamicin treatment. Variables used in estimating pharmacokinetic parameters consists of response variables and predictor variables. The response variable is gentamicin concentration in serum (y), while the predictor variable is the time of sampling (t) and the initial dose position (D).

The steps are taken in carrying out data analysis to do individual dosing using PKBUGS. PKBUGS has been developed by Dave Lunn when at the Department of Epidemiology and Public Health of Imperial College at St Mary's Hospital London. It is an add-on to WinBUGS that fits pharmacokinetic models and MATLAB software is as follows.

- Enter the number of gentamicin concentrations in 13 patients.
- Describe pharmacokinetic factors.
- Modeling data with one compartment population pharmacokinetic model, namely Equation (1).
- Estimate pharmacokinetic parameters V and Cl with PKBUGS. The steps estimation with PKBUGS is as follows.
- Individual pharmacokinetic parameters estimation V and Cl with individual pharmacokinetic models of one compartment using a MAP with the following steps.
- Determine the interval dose for each patient.

4. Result

4.1. Validation of the pharmacokinetic model with the bayesian approach

Validation of the pharmacokinetic model was conducted to determine the feasibility of the model obtained by the Bayesian approach in predicting the concentration of gentamicin in the blood. The data used in this validation stage are 9 data in samples and 4 data out samples. Sample data is used to model individual pharmacokinetics while out sample data is used to validate the results of predictions obtained from the results of modeling the in samples data.

The analysis begins with determining the prior information in sample data in the form of population pharmacokinetic parameter estimation using open source PKBUGS package code program. The prior information obtained is shown in the following model.

$$y = \frac{D}{16.98115} e^{-0.17196}$$

The prior information produced is then used to assess individual pharmacokinetic parameters. In addition, laboratory error patterns are also used in assessing individual pharmacokinetic parameters. The pattern of laboratory errors used is $\hat{s}_d(y_{ij}) = 0.035742 - 0.011443 y_{ij} + 0.0020805 y_{ij}^2$. Thus, the results of individual pharmacokinetic parameters are obtained from the out sample data shown in Table 1.

Table 1. Prediction of individual gentamicin concentrations.

Individual	V (L)	Cl (L/hours)	k (hours-1)
10	33,0153	4,6816	0,1418
11	18,5794	3,8088	0,2050
12	20,2520	0,6967	0,0344
13	7,2090	2,1894	0,3037

The results of parameter estimation in Table 1 are used to predict gentamicin concentration. Gentamicin concentration prediction is presented in Table 2.

Table 2. Prediction of individual gentamicin concentrations.

Individual	Time (hours)	Prediction (mg/L)	Observation (mg/L)
10	4.58	1.266	1.270
	7.17	0.877	0.895
11	5.00	1.545	1.545
	7.00	1.025	1.030
12	4.83	3.346	3.355
	7.00	3.105	3.115
13	6.67	1.464	1.455
	8.00	0.977	0.945

Table 2 shows the results of predictions of the 10^{th} to 13^{th} individual gentamicin concentrations at certain hours that are not much different from the observation. Mean Square Error (MSE) is 0.0002 and the coefficient of determination r^2 is 100%. Thus. It can be ascertained that Bayesian modeling of individual pharmacokinetics is appropriate.

4.2. Pharmacokinetic modeling uses all data

The validation phase has proven that Bayesian modeling of individual pharmacokinetics is feasible to use. Thus, the dosage setting stage of the drug is done by modeling the entire data using Bayesian individual pharmacokinetics.

The first step is to estimate population pharmacokinetic parameters using all data. The results of the population pharmacokinetic parameters are:

$$y = \frac{D}{19,92870} e^{-0.13551t}$$

The second step is to estimate individual pharmacokinetic parameters based on the results of the estimation of population pharmacokinetic parameters. Fig. 1 shows the results of estimating individual pharmacokinetic parameters.

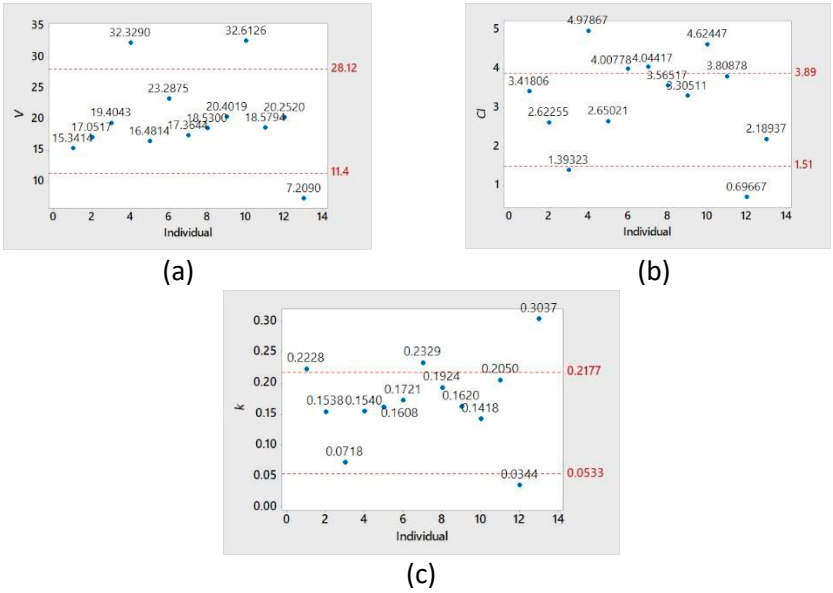

Fig. 1. (a) Estimation of individual pharmacokinetic parameters V; (b) Estimation of individual pharmacokinetic parameters Cl; (c) Estimation of individual pharmacokinetic parameters k.

Fig. 1 shows that some patients have pharmacokinetic parameters outside the interval of the population parameters. Based on the estimated value of the pharmacokinetic parameters. Fig. 1.a represents three individuals who have parameter V exceeding the upper and lower limits of the population parameter, including the 4th individual, 10th individual, and 13th individual. Fig. 1.b shows that 6 individuals have Cl exceeding the population interval, as well as Fig. 1.c which shows that there are 4 individuals who have a parameter k exceeding the population interval. The individual pharmacokinetic model for the 1st patient is:

$$y = \frac{D}{15.3414} e^{-0.222800t}$$

The final step is to predict the concentration of gentamicin in each individual and then dosing the drug based on the results of the prediction. The peak level used in this dosing is the lower limit of 4 $\mu g / ml$ and the upper limit is equal to 4 $\mu g / ml$ with the peak time for one hour. The dosage range obtained can be represented in Fig. 2.

Fig. 2 shows that not all the patients will be suitable if given a dose of 80 mg (initial gentamicin dose injected in urological surgery patients). Overall the 13 patients observed only three patients received dose according to the patient's body condition. These patients are the 2nd, the 3rd, and the 12th.

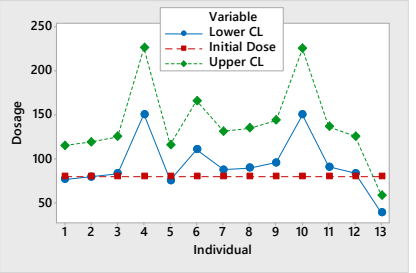

Fig. 2. Individual dosage.

5. Conclusion

The results of model validation obtained using the Bayesian approach to individual pharmacokinetics show that this method is suitable for obtaining estimates of pharmacokinetic parameters in cases of gentamicin giving to urological surgery patients. This is indicated by MSE is 0.0002 and the coefficient of determination is 100%. In addition, the range of doses that must be given to each patient should vary according to the patient's body condition. In this case, the 4th and 10th patients should get a higher dosage than other patients, while the 13th patient should get a smaller dosage than other patients.

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