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Unique	Improper dosing may worsen the disease or even can cause death	-
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Unique	Improper dosing may worsen the disease or even can cause death	-
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Unique	id 594 Brina Miftahurrohmah et al	-
Unique	A field of science that has been developed to overcome this problem is pharmacokinetics	-
Unique	Drug dosing should not only be done by dosing the population but also individually	-
Unique	The pharmacokinetic model analyzed was an open compartment model	-
Unique	Furthermore, the result parameters from individual assessments will be used for individual dosing	-
Unique	The simplest pharmacokinetics model is one compartment model	-

Unique	Population pharmacokinetic modelling The Bayesian model developed from the Bayes method	-
Unique	The basis of this method is Bayes theorem	-
Unique	The main problems in set entered into prior distribution and distribution posterior character produced	-
Unique	One of the most important and well-known MCMC methods is Gibbs Sampler	-
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Unique	However, it might take a long time 596 Brina Miftahurrohmah et al	-
Unique	On the second stage hierarchy model, the distribution assumption is as follows	-
Unique	From the third stage, iterations will be carried until converged	-
Unique	In this case, the expected value to be converged is	-
Unique	This is done because the value will be used to determine pharmacokinetic parameters	-
Unique	Methodology The data used in this research is secondary data taken from [10]	-
Unique	Variables used in estimating pharmacokinetic parameters consists of response variables and predictor variables	-
Unique	Enter the number of gentamicin concentrations in 13 patients	-
Unique	Describe pharmacokinetic factors	-
Unique	Modeling data with one compartment population pharmacokinetic model, namely Equation (1)	-
Unique	Estimate pharmacokinetic parameters V and Cl with PKBUGS	-
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Unique	The prior information obtained is shown in the following model	-
Unique	In addition, laboratory error patterns are also used in assessing individual pharmacokinetic parameters	-
Unique	Prediction of individual gentamicin concentrations	-
Unique	Gentamicin concentration prediction is presented in Table	-
Unique	Prediction of individual gentamicin concentrations	-
Unique	It can be ascertained that Bayesian modeling of individual pharmacokinetics is appropriate	-
Unique	The first step is to estimate population pharmacokinetic parameters using all data	-
Unique	1 shows the results of estimating individual pharmacokinetic parameters	-
Unique	(a) Estimation of individual pharmacokinetic parameters	-
Unique	(b) Estimation of individual pharmacokinetic parameters Cl	-
Unique	(c) Estimation of individual pharmacokinetic parameters	-
Unique	Based on the estimated value of the pharmacokinetic parameters	-
Unique	b shows that 6 individuals have Cl exceeding the population interval, as well as Fig	-
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Unique	600 Brina Miftahurrohmah et al	-
Unique	This is indicated by MSE is 0.0002 and the coefficient of determination is 100%	-
Unique	(2009) “Determination Of Pharmacokinetic Prior Distribution Using NPAG Algorithm In Matlab	-
Unique	” [Master Thesis], Surabaya, Institut Teknologi Sepuluh Nopember	-
Unique	” Therapeutic Drug Monitoring 22 (6) : 676-687	-
Unique	” Therapeutic Drug Monitoring 27 (3) : 554-561	-
Unique	D (2008) “Population And Individual Pharmacokinetics Modeling Using Nonparametric-Em Algorithm And Bayesian Analysis	-
Unique	” [Master Thesis], Surabaya, Institut Teknologi Sepuluh Nopember	-
Unique	” [Dissertation], Surabaya, Universitas Airlangga	-
Unique	(2008) Applied Clinical Pharmacokinetics (2 ed	-
Unique	” Encyclopedia of Environ-metrics 3 : 1634-1637	-
Unique	(2013) “A Bayesian Population Pharmacokinetic	-
Unique	” [Master Thesis], Rotterdam, Erasmus University Rotterdam	-
Unique	” [Master Thesis] Surabaya, Universitas Airlangga	-
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Unique	Model Approach Brina Miftahurrohmah a , Nur Iriawan b, , Catur Wulandari a , Yogantara	-
Unique	Surabaya 60111, Indonesia Abstract Giving the right dose of medicine is very important in the	-
Unique	Drug dosing should not only be done based on the population because each individual	-
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Unique	Introduction The drug is an important component in health because the drug is needed	-
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Unique	Procedia Computer Science 161 (2019) 593–600 2 Author name Procedia Computer Science	-
Unique	This method is studying drug movement in the human body, starting from the process	-
Unique	ADME process in the body could be described as a mathematics relationship in the	-
Unique	The process description could be in the form of one model compartment and two	-
Unique	This is done because each individual has a different characteristic viewed from factors that	-
Unique	Different pharmacokinetics characteristic in each individual allows different dosages to be received by each	-
Unique	Several studies have been developed to estimate the value of pharmacokinetic parameters, both in	-
Unique	three models of population pharmacokinetics flucytosine (5-FC) using Standard Two-Stage (STS), Nonparametric Expectation Maximization (NPEM)	-
Unique	The results of the analysis stated that NONMEM is the most reliable and accurate	-
Unique	[3] conducted a study stating that the NPAG algorithm applied pharmacokinetic parameters iteration faster	-
Unique	A Posteriori (MAP) on the pharmacokinetics of mycophenolic acid is capable of accurately estimating inter	-
Unique	The analysis carried out stated that the MAP-Bayesian estimator of mycophenolic acid systemic exposure	-
Unique	[5] modeling individual pharmacokinetics in patients receiving injections gentamicin by the population with NPEM	-
Unique	Furthermore, [1] also analyzed with the same data, but what is done is to	-
Unique	slop of K for kidney function, creatinine clearance (Ks) Vs V, where pharmacokinetics using the	-
Unique	pharmacokinetic parameters where the pharmacokinetic parameters obtained from the population will be used to estimate	-
Unique	of the population and individuals in the case of gentamicin administration to urological surgery patients	-
Unique	are differences in the stages of modeling population pharmacokinetic parameters that place more emphasis on	-
Unique	Pharmacokinetics Pharmacokinetics study drug movement drug in the human body starting from the process	-
	The pharmacokinetic model can provide a more rigorous interpretation of the	

Unique	relationship between drug	-
Unique	Cl is the clearance, k is the elimination rate constant and t is the time	-
Unique	tij is the peak time of the drug on the ith individual at the jth	-
Unique	parameters which combined with new data probability distribution to produce posterior distribution which is used	-
Unique	In terms of the large sample size and parameter identified, a reasonable choice from	-
Unique	sample and □ □ px is normalized constant which can be ignored [5] so that	-
Unique	p x Lx p □ □ □ □ (5) One of the modeling techniques	-
Unique	Gibbs Sampler has based on the characteristic that a multivariate distribution is unique which	-
Unique	For pharmacokinetic cases, it means □ □ □ ,, V Cl □ □ so	-
Unique	p V Cl y □ Gibbs Sampler will help estimate parameters ,V □ Cl	-
Unique	Sample (1) k □ □ from □ □ ( ) ()		-
Unique	Sample (1) k V □ from □ □ (1) ( )	-
Unique	Sample (1) k Cl □ from □ □ (1) ( )	-
Unique	)	,, kk p Cl Cl y □ □ □ is posterior marginal for	-
Unique	Cl Thus Markov chain is obtained which means ( ) (1) , kk	-
Unique	It is proven that samples from the posterior distribution achieved by following the Gibbs	-
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Unique	the Gibbs	
Unique	00 (2019) 000–000 for convergence and sample algorithms from the posterior distribution, therefore the initial	-
Unique	In the case of pharmacokinetics, if only drug concentration in plasma is observed in	-
Unique	observations of individual i () ij y and related to the time of observation ()	-
Unique	Vector pharmacokinetic parameters for individuals i denoted by i □ with size 1 p□	-
Unique	| ,) ~ (,), ij i ij ij py N f	-
Unique	equal to i □ □ , that is (,) ij ij ft □ and	-
Unique	Note that other distributions other than normal distribution may be selected, such as lognormal	-
Unique	□ is pharmacokinetics population behavior () pp □ □ is variance- covariance matrix representing an	-
Unique	In the third stage, the hierarchy model can be shown by setting prior density	-
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Unique	Pharmacokinetics modeling individual i th The analysis method used for the drug dose individualization	-
Unique	d ij sy estimated using a second order regression model that stated the drug concentration	-
Unique	ij ij ij sy y y □□ □ □□□ (12) The function is a laboratory	-
Unique	The process of MAP optimization is done by the Nelder-Mead Simplex iteration, namely by	-
Unique	The subjects studied were 13 urological surgery patients at Syaiful Anwar Malang Hospital who	-
Unique	The response variable is gentamicin concentration in serum (y), while the predictor variable is	-
Unique	The steps are taken in carrying out data analysis to do individual dosing using	-
Unique	PKBUGS has been developed by Dave Lunn when at the Department of Epidemiology and	-
Unique	It is an add-on to WinBUGS that fits pharmacokinetic models and MATLAB software is	-
Unique	□ Individual pharmacokinetic parameters estimation V and Cl with individual pharmacokinetic models of one	-
Unique	was conducted to determine the feasibility of the model obtained by the Bayesian approach in	-
Unique	The data used in this validation stage are 9 data in samples and	-
Unique	to validate the results of predictions obtained from the results of modeling the in samples	-

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Unique	00 (2019) 000–000 The analysis begins with determining the prior information in sample data in	-
Unique	0.17196 16.98115 D ye □ □ The prior information produced is then used to	-
Unique	The pattern of laboratory errors used is 2 ˆ ( ) 0.035742 0.011443 0.0020805	-
Unique	d ij ij ij sy y y □ □□ Thus, the results of individual	-
Unique	0.2050 12 20.2520 0.6967 0.0344 13 7.2090 2.1894 0.3037 The results of parameter estimation in	-
Unique	10 th to 13 th individual gentamicin concentrations at certain hours that are not much	-
Unique	Mean Square Error (MSE) is 0.0002 and the coefficient of determination 2 r is	-
Unique	Pharmacokinetic modeling uses all data The validation phase has proven that Bayesian modeling of	-
Unique	Thus, the dosage setting stage of the drug is done by modeling the entire	-
Unique	to estimate individual pharmacokinetic parameters based on the results of the estimation of population pharmacokinetic	-
Unique	1 shows that some patients have pharmacokinetic parameters outside the interval of the population	-
Unique	a represents three individuals who have parameter V exceeding the upper and lower limits of	-
Unique	c which shows that there are 4 individuals who have a parameter k exceeding the	-
Unique	ye □ □ The final step is to predict the concentration of gentamicin in each	-
Unique	g ml □ and the upper limit is equal to 4 g ml	-
Unique	2 shows that not all the patients will be suitable if given a dose	-
Unique	Overall the 13 patients observed only three patients received dose according to the patient's	-
Unique	These patients are the 2 nd , the 3 rd , and the 12	-
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Unique	Procedia Computer Science 161 (2019) 593–600 8 Author name Procedia Computer Science	-
Unique	show that this method is suitable for obtaining estimates of pharmacokinetic parameters in cases of	-
Unique	In addition, the range of doses that must be given to each patient should	-
Unique	than other patients, while the 13 th patient should get a smaller dosage than other	-
Unique	(2000) “Population Pharmacokinetics of Flucytosine: Comparison and Validation of Three Models Using STS, NPEM,	-
Unique	(2001) “An Adaptive Grid Non-Parametric Approach to Pharmakicinetic and Dynamic (PK/PD) Population Models”, in	-
Unique	(2005) “Maximum A Posteriori Bayesian Estimation of Mycophenolic Acid Pharmacokinetics in Renal Transplant Recipients	-
Unique	[Title in English: Modelling Population Pharmacokinetics of Amikacin for Single Study Dose Regiment in Orthopedic	-
Unique	(1997) “Farmakokinetika Populasi dari Gentamisin: Studi Pada Pasien Bedah Urologi [Title in English: Population	-
Unique	13 12 11 10 9 8 7 6 5 4 3 2 1 250	-

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The Fifth Information Systems International Conference 2019 Individual Control Optimization of Drug Dosage Using Individual Bayesian Pharmacokinetics Model Approach

Brina Miftahurrohmah a , Nur Iriawan b, *, Catur Wulandari a , Yogantara Setya Dharmawan a a Universitas Internasional Semen Indonesia, Komplek PT. Semen Indonesia (Persero) Tbk. Jl. Veteran, Gresik 61122, Indonesia b Institut Teknologi Sepuluh Nopember, Kampus Institut Teknologi Sepuluh Nopember, Surabaya 60111, Indonesia

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. Peer-review under responsibility of the scientific committee of The Fifth Information Systems International Conference 2019 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 * Corresponding author. Tel.: +62-818-513-626. E-mail address: nur_i@statistika.its.ac.id Available online at www.sciencedirect.com ScienceDirect Procedia Computer Science 00 (2019) 000–000 www.elsevier.com/locate/procedia 1877-0509 © 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/) Peer-review under responsibility of the scientific committee of The Fifth Information Systems International Conference 2019 The Fifth Information Systems International Conference 2019 Individual Control Optimization of Drug Dosage Using Individual Bayesian Pharmacokinetics Model Approach Brina Miftahurrohmah a , Nur Iriawan b, *, Catur Wulandari a , Yogantara Setya Dharmawan a a Universitas Internasional Semen Indonesia, Komplek PT. Semen Indonesia (Persero) Tbk. Jl. Veteran, Gresik 61122, Indonesia b Institut Teknologi Sepuluh Nopember, Kampus Institut Teknologi Sepuluh Nopember, Surabaya 60111, Indonesia 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. © 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/) Peer-review under responsibility of the scientific committee of The Fifth Information Systems International Conference 2019 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 * Corresponding author. Tel.: +62-818-513-626. E-mail address: nur_i@statistika.its.ac.id 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: kt D ye V □ □ (1) with Author name / Procedia Computer Science 00 (2019) 000–000 3 Cl k V □ (2) where y is the drug concentration at time t, □□ 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 □□ ˆ ˆ ˆ ˆ exp ij i i i ij yV D kt □ □ (3) where □□□ is an ith individual dose estimation, □□□ □□ is the peak concentration of the drug on the ith individual on jth observation, □□□ □ is the volume of distribution on the ith individual □□□ , 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 □□ □ □ □ □ □□ | | Lx p px px □ □ □ □ (4) which □ □ □ ,, V Cl □ □ , □ □ | px □ is posterior distribution, □ □ p□ is prior distribution, □ □ | Lx□ is likelihood value from the sample and □ □ px is normalized constant which can be ignored [5] so that posterior distribution can be written □ □ □ □ □ □ | |. p x Lx p □ □ □ □ (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 □ □ □ ,, V Cl □ □ so the posterior form of the joint is □ □ ,, | . p V Cl y □ Gibbs Sampler will help estimate parameters ,V □ Cl and iteratively by following the sampling scheme as follows. 1. Sample (1) k □ □ from □ □ ( ) () | , ,. kk p V Cl □ y 2. Sample (1) k V □ from □ □ (1) ( ) | , ,. kk p V Cl □ □ y 3. Sample (1) k Cl □ from □ □ (1) ( ) | , ,. kk p Cl Cl □ □ y Where □ □ () () |, , kk p V Cl y □ □ , □ □ (1) ( ) | ,, kk p V Cl y □ □ □ and □ □ (1) ( ) | ,, kk p Cl Cl y □ □ □ is posterior marginal for ,V □ and . Cl Thus Markov chain is obtained which means ( ) (1) , kk □ □ □ (1) (2) , ,... kk □□ □ □ 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 Brina Miftahurrohmah et al. / Procedia Computer Science 161 (2019) 593–600 595 2 Author name / Procedia Computer Science 00 (2019) 000–000 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. 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However, it might take a long time 596 Brina Miftahurrohmah et al. / Procedia Computer Science 161 (2019) 593–600 4 Author name / Procedia Computer Science 00 (2019) 000–000 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 (1,...,) iK □ , the concentration of drug in the body to k th observations of individual i () ij y and related to the time of observation () ij t . Vector pharmacokinetic parameters for individuals i denoted by i □ with size 1 p□ or 12 (, ,...,) T ip □□ □ □ □ . In the first stage of the hierarchy model, the form of opportunity distribution of each ij y in the form of i □ and □ certain like 1 (| ,) ~ (,), ij i ij ij py N f v □□ □ □ for 1,..., iK □ 1,..., i jn □ (6) with 1 ~ (,), ij ij ij y Nf v □ □ conditional i □ □ and □ (distance between dosages), ij f is a pharmacokinetic model that has been evaluated on ij t with individual pharmacokinetic parameters equal to i □ □ , that is (,) ij ij ft □ and ij v 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. 1 (| ,) ~ (,), ip pN □ □ □ □ □ □ for 1,..., iK □ (7) with p N is a normal multivariate distribution (1) p□ □ is pharmacokinetics population behavior () pp □ □ 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 □□,□□ dan □□. ( ) (,), pG □ □□ □ (8) ( ) (,) p pN □ □ □c (9) □ □ 11 () , p pW □ □□ □ □ R (10) with (,) G□□ is a gamma distribution with parameters □ □ and, (1) p□ □ is a □ prior estimation with covariant- variant matrix c and p W shows a p-dimension of Wishart distribution with an average 1 () pp □ □ R and free degree □ [9]. From the third stage, iterations will be carried until converged. In this case, the expected value to be converged is □ . This is done because the value□ will be used to determine pharmacokinetic parameters. The results of the estimation of pharmacokinetic population parameters are exponential values□ , with 2 exp( ) V □ □ a while 1 exp( ) Cl □ □ . 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: □ □ □□ □ □ 2 2 2 22 1 ˆˆ ˆ ˆ (,) ˆ ˆˆ ( ) ( ) () U ij i ij i i d ij d d i y f t kk VV MAP s y sV s k □ □ □□ □ □ □□ □ □ (11) where U = number of drug concentration measurement on the i th individual ij y = individual drug concentration data on the i th individual at the j th observation Author name / Procedia Computer Science 00 (2019) 000–000 5 ˆ ˆ (,) i ij ft □ □ = pharmacokinetic predictive models on individual i th , which has been evaluated at ij t V = volume of population distribution k = rate of population elimination ˆ V = predictive value of the volume of distribution on i th individual ˆ i k = prediction of the value of the elimination rate in the i th individual ˆ () d ij sy = deviation standard of drug concentration in the i th population ˆ () d sV = standard deviation of the volume of distribution of the i th population ˆ () d sk = standard deviation of the i th population elimination rate Function ˆ () d ij sy estimated using a second order regression model that stated the drug concentration observed in serum. The function can be written as 2 01 1 ˆˆ ˆ ˆ () d ij ij ij sy y y □□ □ □□□ (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. Brina Miftahurrohmah et al. / Procedia Computer Science 161 (2019) 593–600 597 4 Author name / Procedia Computer Science 00 (2019) 000–000 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 (1,...,) iK , the concentration of drug in the body to k th observations of individual i () ij y and related to the time of observation () ij t . Vector pharmacokinetic parameters for individuals i denoted by i with size 1 p or 12 (, ,...,) T ip   . In the first stage of the hierarchy model, the form of opportunity distribution of each ij y in the form of i and certain like 1 (| ,) ~ (,), ij i ij ij py N f v   for 1,..., iK 1,..., i jn (6) with 1 ~ (,), ij ij ij y Nf v   conditional i   and (distance between dosages), ij f is a pharmacokinetic model that has been evaluated on ij t with individual pharmacokinetic parameters equal to i   , that is (,) ij ij ft and ij v 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. 1 (| ,) ~ (,), ip pN   for 1,..., iK (7) with p N is a normal multivariate distribution (1) p is pharmacokinetics population behavior () pp   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 , dan . 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The function can be written as 2 01 1 ^^ ^ ^ () d ij ij ij sy y y   (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

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The prior information obtained is shown in the following model. 0.17196 16.98115 D ye   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 2 ˆ ( ) 0.035742 0.011443 0.0020805 . d ij ij ij sy y y   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 2 r 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: Author name / Procedia Computer Science 00 (2019) 000–000 7 0.13551 19,92870 t D ye   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. (a) (b) (c) 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 4 th individual, 10 th individual, and 13 th individual. 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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 1 st patient is: 0.222800 15.3414 t D ye □ □ 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 / g ml □ and the upper limit is equal to 4 / 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 2 nd , the 3 rd , and the 12 th . 600 Brina Miftahurrohmah et al. / Procedia Computer Science 161 (2019) 593–600 8 Author name / Procedia Computer Science 00 (2019) 000–000 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 4 th and 10th patients should get a higher dosage than other patients, while the 13 th patient should get a smaller dosage than other patients. References [1] Gunawan. 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Osch, P. V. (2013) “A Bayesian Population Pharmacokinetic.” [Master Thesis], Rotterdam, Erasmus University Rotterdam. [10] Suprapti B. (1997) “Farmakokinetika Populasi dari Gentamisin: Studi Pada Pasien Bedah Urologi [Title in English: Population Pharmocokinetics from Genmatisin: A Stuady in Urology Surgery Patients].” [Master Thesis] Surabaya, Universitas Airlangga. 13 12 11 10 9 8 7 6 5 4 3 2 1 250 200 150 100 50 Individual Dosage Lower CL Initial Dose Upper CL Variable