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Research Article

DEVELOPMENT CONCEPT OF PHARMACOKINETICS SIMULATION TO PREDICT CHRONOKINETICS PROFILE OF DIGOXIN ON MULTIPLE DOSAGE REGIMEN

Made Krisna Adi Jaya*, Dewa Ayu Swastini, I.M.A Gelgel Wirasuta

Department of Pharmacy, Faculty of Math and Science, Udayana University, Bali-Indonesia

*Corresponding Author Email: krisnaadijaya598@gmail.com

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ABSTRACT

Background: Pharmacokinetic simulation is a method that can be used to estimate the concentration profile of drugs in blood, especially in determining the level of drug safety. One of the phenomena related to drug safety is chronopharmacokinetic. Chronopharmacokinetic can cause deviations in drug kinetics profiles due to biological rhythms. This is important to note especially in narrow therapeutic index drugs such as digoxin, because sudden changes in drug kinetics are very susceptible to toxic effects. Strengthening the concept of this phenomenon is needed through the development of a simulation model of chronopharmacokinetic digoxin in multiple-doses. Methods: A pre-experimental study of a one shot case study approach was carried out. The case's data were then be remodeled, re-simulated, and re-analyzed in accordance with the concept of simulation development. Result: The digoxin pharmacokinetics equation on average at 07.00 AM is $PC = 1.667\ e^{-0.418.t} + 0.986\ e^{-0.022.t} - 0.860\ e^{-1.519.t}$ and at 04.00 PM is $PC = 1.438\ e^{-0.562.t} + 1.354\ e^{-0.020.t} - 1.066\ e^{-1.098.t}$. The results of statistical tests of digoxin kinetic parameters showed, volume distribution (VD) was significantly higher in the morning compared to the afternoon. Absorption rate, elimination, drug clearance, digoxin at 07.00 AM have a higher tendency than at 04.00 PM, while the half-life of elimination, AUC, steady-state plasma concentrations tend to be lower at 07.00 AM compared to 04.00 PM. Conclusion: Modeling the deviation of the drug kinetics profile was successfully developed. The Chronopharmacokinetic phenomenon needs to be watched out especially on drugs with a narrow therapeutic index.

Keywords: Pharmacokinetics Simulation, Chronopharmacokinetic, Digoxin, Multiple Dosage Regimen, Pharmacokinetics Modelling.

INTRODUCTION

Pharmacokinetic simulation is a method that can be used to estimate the concentration profile of drugs in blood or other biological specimens, especially on determining the level of drug safety[1]. In addition, pharmacokinetics simulation methods are also used in forensic toxicology cases to estimate drug pharmacokinetics deviations that can harm an individual.[1,2] One of the important drug kinetics deviations is chronopharmacokinetic phenomena. Chronopharmacokinetic is a condition that can cause a deviation in the profile of the drug kinetics due to the influence of temporal or biological rhythms. This phenomenon is important to be focused on drugs with a narrow therapeutic index.[3]

Digoxin is one of the drugs with a narrow therapeutic index that is widely used for heart disease. The digoxin plasma concentration must be between 0.4 - 4.0 ng/mL to maintain its effectiveness.[4,5] Therapeutic Drugs Monitoring (TDM) of digoxin is highly recommended because of the toxic effects that often occur in sufferers. This drug was reported to be affected by the chronopharmacokinetic phenomenon.[4] In a previous study, it was reported that there was a significant difference in digoxin profile given in the morning (07.00 AM) compared to late afternoon (04.00 PM) in the blood of patients with congenital heart failure, but it was not clearly described how the digoxin profile was given with a multiple-dose regimen.[5] The development of a chronopharmacokinetic simulation model is needed to facilitate understanding of this phenomenon.

In this study, a chronopharmacokinetic simulation method of digoxin was developed with a multiple-dose regimen. By conducting this research, it is expected to provide an overview for health workers (doctors, pharmacists, nurses) on predicting digoxin chronopharmacokinetic phenomena through simulation. Therefore they can used this concept as references, on carrying out appropriate pharmacological therapy and minimize toxic effects of digoxin when given repeatedly.[6,7]

MATERIAL AND METHODS

Study Design

The design of this study was a pre-experimental study of a one shot case study approach, in which the use of secondary data obtained from a case in a publication related to chronopharmacokinetic of digoxin.[5] The secondary data were then be remodeled, re-simulated, and reanalyzed in accordance with the concept of simulation development, so that it can be used to predict its profile when given in multiple regimen.

Material

The materials used in this study include: Micro math scientist version 3.0 used for data fitting processes, Microsoft excel used for designing pharmacokinetics models and calculating mathematical equations, SPSS was used to analyze the statistics of pharmacokinetics data.

Data Source

Secondary data were taken from a study by Liu, *et al*., 1998 entitled "Clinical Study on Chronopharmacokinetic of Digoxin in Patients with Congestive Heart Failure".[5] This study used 20 human subjects with congestive heart failure who received digoxin therapy with the same dose and frequency (0.25 mg per day). 10 subjects were given digoxin therapy at 07.00 AM, and 10 other subjects were given at 04.00 PM. Digoxin kinetic profile was evaluated between groups.

Pharmacokinetics Models

The pharmacokinetics model was developed from a Weiss kinetic metabolite model that utilizes Laplace transformation into input and disposition functions.[1] This model was developed into two open oral compartments combined with the superposition method to simulate the profile of multiple-dose regimen. The model in question is shown as follows:

Input function: $\hat{I}_{p,or}(s) = D_{or} . F. \Psi_A(s)$; $\Psi A(s) = \frac{Ka}{s+Ka}$ ..... (1)

Distribution function: $C_{iv}(t) = \sum_{i=1}^{n} \frac{A_i}{(s+\lambda i)}$+.....Cn .....(2)

Formula description: $\hat{I}_{p,or}$ =oral input function; D_{or}= drug dosage; $\Psi_A(s)$=absorption function; Ka=absorption constants; Civ= distribution function; Ai=intercept distribution phase; λi=distribution constants; s=laplace number; Cn=equations for the next phase (depending on the model).

The input function describes the process needed so that the given dose reaches blood circulation; while the distribution function describes the distribution process of the drug in the circulatory system to eliminate it. The distribution function of either intravenous or oral administration is described as a similar function. Then the model was developed into the 3 and 4 equation below:

```
// Pharmacokinetic Simulations
// Oral input
IndVars: T
LaplaceVar: S
DepVars: C
Params: DOSE, F, Ka, A, ALPHA, B, BETA
INPUT=DOSE*F*(Ka/(S+Ka))
DIST=(A/(S+ALPHA)+B/(S+BETA))
CTRAN=INPUT*DIST
C=LAPLACEINVERSE(T, CTRAN, S)
```

.....(3)

$$PC = Ae^{-\alpha.t} + Be^{-\beta.t} - Ce^{-\gamma.}$$

.....(4)

Formula description: PC = plasma concentration; A = intercept of distribution phase; B = intercept of elimination phase; C = intercept of absorption phase; α = distribution constants; β = elimination constants; Ɣ = absorption constants.

Pharmacokinetics Simulation

The simulation steps were carried out as follows: input the digoxin plasma data (at 07.00 AM and 04.00 PM) into Micro math Scientist worksheet. Applied equation 3 in Micro math Scientist and do data fitting to obtain pharmacokinetics equations. After the pharmacokinetics equation is obtained, then arrange according to the form of formula 4. At this stage we can determine primary pharmacokinetics parameters (dose, bioavailability, absorption, distribution, and elimination constant) and secondary parameters (elimination half-life, clearance, AUC, steady-state plasma concentration). The pharmacokinetics equation obtained simultaneously can be used to simulate repeated dosing using the superposition method by Microsoft Excel.

Statistical Analysis

Statistical analysis was performed to test the comparison of the pharmacokinetics parameters of the simulation results (digoxin given at 7:00 AM morning versus 04:00 PM) in the scope of repeated doses. Comparison of t-test and Mann Whitney U were utilized in this study.

RESULT

Fitting Data

Data fitting aims to determine how much correlation between the data simulated and the pharmacokinetics equations obtained. Figure 1 shows that the results of fittings have a correlation of 0.99, both for digoxin data given at 07.00 AM and 04.00 PM. That means the data correlates closely to the simulation.

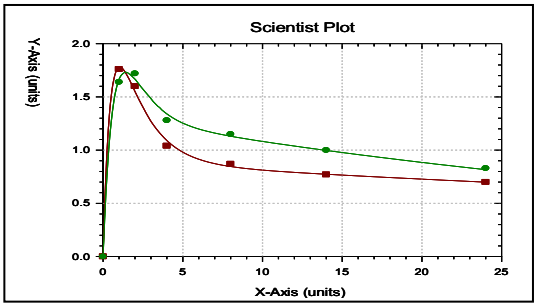

Figure 1: Data Fitting Result. (X-Axis: time (hour), Y-Axis: plasma concentration (ng/mL), ▪: Digoxin 07.00 AM, ●: Digoxin 04.00 PM)

Based on the results of the fittings obtained the digoxin pharmacokinetics equation on average at 07.00 AM is PC = 1.667 $e^{-0.418.t}$ + 0.986 $e^{-0.022.t}$ – 0.860 $e^{-1.519.t}$ and at 04.00 PM is PC = 1.438 $e^{-0.562.t}$ + 1.354 $e^{-0.020.t}$ – 1.066 $e^{-1.098.t}$. This equation can then be used in preparing multiple-dose simulations.

Multiple Doses Simulation

By using the superposition method, multiple-dose simulations was carried out until digoxin reached steady state, i.e. at 10 doses (10 days). Digoxin multiple-dose profile reaches steady state at 4 doses to infinity. The simulation results are shown in Figure 2.

Figure 2 shows that digoxin given at 04.00 PM has a high accumulation profile compared to 07.00 AM. The elimination half-life of digoxin tends to be longer at 04.00. From Figure 2, it can be seen that the administration of afternoon digoxin has the potential to cause toxic effects, because the steady-state plasma concentration approaches the MTC. For further understanding, the digoxin chronokinetics parameters are explored to see the extent of the differences arising from this phenomenon. The kinetics profile in Figure 2 produces pharmacokinetics parameters as showed in Table 1.

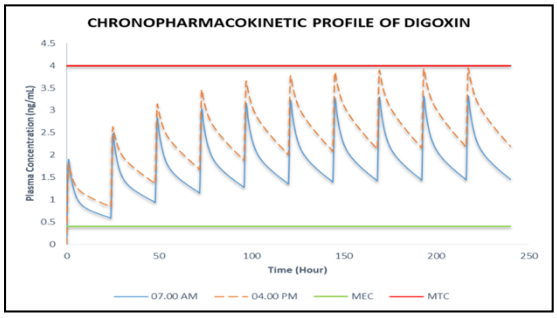

Figure 2: Chronopharmacokinetic profile of Digoxin on multiple-dose regimen
(MEC: minimum effective concentration, MTC: minimum toxic concentration)

The results of calculations and statistical tests of digoxin kinetic parameters indicate that, volume distribution (VD) was significantly different. Other parameters show no difference. The volume of distribution is higher in the morning compared to the afternoon.

Table 1: Digoxin Pharmacokinetic Parameter

Parameter	07.00 AM (Mean ± SD) n = 10	04.00 PM (Mean ± SD) n = 10	Analysis (p-value)	Type of Analysis
A (ng/mL)	1.667 ± 0.987	1.438 ± 1.429	0.682 ns	TT
B (ng/mL)	0.986 ± 0.279	1.354 ± 0.424	0.077 ns	MWU
C (ng/mL)	0.860 ± 0.590	1.066 ± 0.744	0.481 ns	MWU
α (h^{-1})	0.418 ± 0.204	0.562 ± 0.386	0.313 ns	TT
β (h^{-1})	0.022 ± 0.017	0.020 ± 0.014	0.814 ns	TT
Ɣ (h^{-1})	1.519 ± 0.689	1.098 ± 0.551	0.149 ns	TT
T ½ β (h)	32.203 ± 197.545	34.824 ± 95.647	0.642 ns	TT
AUC (ng.h/mL)	49.236 ± 231.771	69.644 ± 141.962	0.529 ns	MWU
VD (mL)	165162.993 ± 43979.998	126270.069 ± 34872.52	0.002 sig.	MWU
CL (mL/h)	3554.308 ± 2028.153	2512.774 ± 1407.908	0.317 ns	TT
Tp (h)	2.237 ± 1.342	2.821 ± 0.9416	0.063 ns	MWU
Css (ng/mL)	2.052 ± 9.657	2.902 ± 5.915	0.529 ns	MWU
Css Max (ng/mL)	2.503 ± 9.612	3.450 ± 5.833	0.315 ns	MWU
Css Min (ng/mL)	1.590 ± 9.683	2.306 ± 5.970	0.436 ns	MWU

Abbreviation: n=subject in research; A = intercept of distribution phase; B = intercept of elimination phase; C = intercept of absorption phase; α = distribution constants; β = elimination constants; Ɣ = absorption constants; T½ β = half life elimination; AUC = area under curve; VD = distribution volume; CL = digoxin clearance; Tp = time to steady state plasma maximum; Css = average steady state plasma concentration; Css Max = maximum steady state plasma concentration; Css Min = Minimum steady state plasma concentration; TT = independent t-test; MWU = Mann Whitney u test; p< 0.05 significant; sig = significant; ns = not significant.

Absorption rate, elimination, drug clearance, digoxin at 07.00 AM have a higher tendency than at 04.00 PM, while the half-life of elimination, AUC, steady-state plasma concentrations tend to be lower at 07.00 AM compared to 04.00 PM. However, all differences in these important parameters were not significantly different.

DISCUSSION

Chronopharmacokinetic is a science that is closely related to changes in biological rhythms and has an impact on physiological processes such as absorption, distribution, metabolism, and elimination of a drug. This study can explain variations in drug kinetics in the human body, and provide an overview of the pharmacological effects of drugs that are affected by circadian rhythms.[6–8]

Changes in temporal drug absorption (within 24 hours) in the gastrointestinal tract can be affected by gastric acid secretion, changes in gastric pH, gastrointestinal motility, gastric emptying time, and blood flow rate. Gastrointestinal activity tends to be optimal in the morning and will slow down in the late afternoon.[7,9] The high motility and rate of blood flow in the gastrointestinal tract in the morning will cause a higher rate of absorption and bioavailability of the drug than in the afternoon. This condition is in accordance with the simulation results which show that the absorption rate of digoxin is higher at 07.00 AM, although statistically it is not different from 04.00 PM.[2,9]

The process of drug distribution in the body depends on the state of activity and rest, the rate of vascular blood flow, and tissue perfusion. These things have an impact on the binding of drugs to plasma proteins, receptor drug bonds, and changes in the volume of distribution in the body. The distribution process is also optimal in the morning, so that the drug bond with proteins, receptors and the volume of drug distribution will tend to be higher in the morning.[3,6] This condition shows something similar to the simulation results, where VD digoxin in the morning is significantly more significant than the afternoon. The high value of VD causes high drug distribution to peripheral compartments

so that plasma concentrations in the central compartment are relatively lower.[7,8,10]

In terms of elimination (metabolism and excretion), changes in circadian rhythms have an impact on hepatic enzyme activity, blood flow rate in the liver, glomerular filtration rate, pH of tubular re-absorption and changes in urine pH in the kidneys. This physiological process will affect hepatic clearance, renal clearance, elimination half-life, elimination rate, and total number of drugs in the body (AUC).[6–8,10] In the morning, hepatic and renal activity is in optimal condition, so drug clearance and the rate of elimination will have a higher tendency which will result in shorter half-life of elimination and low AUC values. This condition is also in line with the simulation results showing higher clearance profile and digoxin elimination rate at 07.00 AM and lower elimination half-life profile and AUC compared to 04.00 PM.[3,8]

In the simulation conditions, the statements are theoretically relevant to the results, even though most differences in the kinetic parameters are not clinically significant. For drugs with a broad therapeutic index, we can ignore the chronopharmacokinetic phenomenon. However, this phenomenon remains to be watched out for drugs with a narrow therapeutic index.[7,9,10] This study has several limitation such as, the model is only limited to assuming a linear compartment model (no drug interactions, no enzyme saturation, liver, kidney, and heart disorders), this model cannot be used to simulate non-linear and non-compartment conditions, and this study was a pre-experimental using secondary data. With all these limitations, this model can provide an overview of how the chronokinetics phenomenon affects the administration of multiple-dose drugs.

CONCLUSION

Modeling the deviation of the drug kinetics profile was successfully developed by adopting the Weiss kinetics metabolite model combined with the superposition method on the chronopharmacokinetic digoxin phenomenon. Simulation with this model shows that, there was a significant difference in VD digoxin given in the morning compared to the afternoon. This phenomenon needs to be watched out especially on drugs with a narrow therapeutic index.

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