The Concentration of Digoxin Activity after Intravenous in Three Compartments Mathematical Model

Lakshmi Narayan. K, Siva Rama Krishna Reddy. V

Abstract: Present paper is designed to compare the distribution of digoxin in three compartment model administered through an intravenous (i.v). These models under consideration is denoted by a system of non-linear ordinary differential equations. The Eigenvalue and the Laplace transform methods were used to solve the system of equations. Digoxin was administered to five subjects through Intravenous then, the serum digoxin concentrations were measured respectively over a period of 72 hours. The transfer coefficients were obtained from observed digoxin concentrations using method of residuals and the variation of digoxin concentration – time curves plotted using MATLAB.

Index Terms: Digoxin, Blood plasma, Intestinal fluid, Cells, Laplace transform, Eigenvalue,

I. INTRODUCTION

The elucidation of the simplest pharmacokinetic model compatible with the data observed when prescribing drugs in humans is a necessary step to understand the distribution, elimination, activity and toxicity of the drug. This is becoming increasingly important with low therapeutic index drugs and serious side effects such as cardiac digoxin glycoside.

The purpose of this study was to perform an experiment in human designed to compare adjustments of an open pharmacokinetic model to two and three compartments with experimentally determined time-serum digoxin concentration data.

Previous research reported in the literature [1-2] graphical analysis of the blood concentration of digoxin versus time after intravenous administration in humans has shown that a semi-logarithmic plot can be divided into two or three exponential segments, the choice being dependent on blood sampling intervals and graphic techniques used. These analyzes also imply that a two or three compartment model can best describe the temporal evolution of digoxin in humans. In this study, we used the same set of experimental data (Table 3.2) to fit the three compartment model. The transfer coefficients were obtained from observed digoxin concentrations (Table 3.4) using method of residuals and the variation of digoxin concentration – time curves plotted in two and three compartment models of each subject (Table 3.1) using MATLAB.

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II. THREE COMPARTMENT MODEL

In the present model, we consider a three compartment catenary model in which the first compartment is connected to the second compartment and the second compartment is connected to the third compartment, a single dosage of drug flow via first compartment to second compartment, also from second compartment to third compartment and the elimination occurs from last compartment. The first compartment corresponds to blood plasma then from there the drug diffuses into the second compartment namely intestinal fluid and finally it enters into third compartment of Cells as shown in Figure 2.1.

Let $x_1(t), x_2(t)$ and $x_3(t)$ denote the amount of drug in blood plasma compartment, Intestinal fluid compartment and Cells compartment respectively.

Let k_{01} be the initial amount of drug dosage. The mathematical structure of the three compartment system describing the drug administration is given by the set of ordinary differential equations as follows:

$$\frac{dx_1(t)}{dt} = -k_{12}x_1 + k_{21}x_2; \qquad x_1(0) = k_{01} \tag{1}$$

$$\frac{dx_2(t)}{dt} = k_{12}x_1 - (k_{21} + k_{23})x_2 + k_{32}x_3; \quad x_2(0) = 0 \tag{2}$$

$$\frac{dx_3(t)}{dt} = k_{23}x_2 - (k_{32} + k_{20})x_3; \qquad x_3(0) = 0 \tag{3}$$
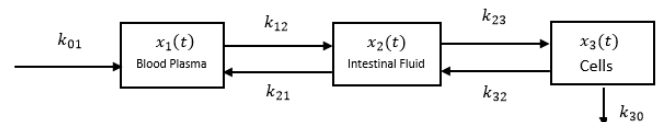
Fig 2.1 General scheme of the three compartment model
Each equation describes the change in drug concentration in their respective compartments over time. Also the quantities k_{12} and k_{21}; k_{23} and k_{32} denote the rate constants from blood plasma compartment to intestinal fluid compartment; intestinal fluid compartment to cells compartment and vice-versa respectively and k_{30} denote the clearance constants from cell compartment only.

In matrix notation of (1), we have

$$\frac{dX}{dt} = KX \tag{4}$$

Where

$$X = \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} \quad and \quad K = \begin{bmatrix} -k_{12} & k_{21} & 0 \\ k_{12} & -(k_{21}+k_{23}) & k_{32} \\ 0 & k_{23} & -(k_{32}+k_{20}) \end{bmatrix} \tag{5}$$

The Laplace transform [3] – [4] is an integral transform where the linear operator $\mathcal{L}\{f(t)\}$ transform a function $f(t)$ with $t \in \mathbb{R}$ from the time domain to a function $F(s)$ with $s \in \mathbb{C}$ in an image domain. The advantage of this transformation is that differentiation and integration in the time domain corresponds to simple algebraic operations in the image domain.

Applying the Laplace transform to (4) gives,

$$\mathcal{L}\{X'(t)\} = \mathcal{L}\{KX\} \iff s\mathcal{L}\{X(t)\} - X(0) = K\mathcal{L}\{X(t)\}$$
$$\iff (sI - K)\mathcal{L}\{X(t)\} = X(0)$$
$$\iff L(s). \mathcal{L}\{X(t)\} = X(0) \tag{6}$$

Where,

$$L(s) = \begin{bmatrix} s+k_{12} & -k_{21} & 0 \\ -k_{12} & s+(k_{21}+k_{23}) & -k_{32} \\ 0 & -k_{23} & s+(k_{32}+k_{20}) \end{bmatrix} \tag{7}$$

We solve the system of equations (6) by Cramer's rule.

$$\det(L(s)) = \det(sI - K)$$
$$= (s+\lambda_1)(s+\lambda_2)(s+\lambda_3)$$

Where,

$$\lambda_1 + \lambda_2 + \lambda_3 = k_{20} + k_{12} + k_{21} + k_{23} + k_{32}$$
$$\lambda_1\lambda_2\lambda_3 = k_{12}(k_{32}+k_{23}) + k_{21}(k_{32}+k_{20}) + k_{20}(k_{23}+k_{12})$$
$$\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_3\lambda_1 = k_{12}k_{23}k_{20}$$

To calculate the solution of the central compartment $x_1(t)$, peripheral compartment $x_2(t)$ and cells compartment $x_3(t)$, we substitute the vector $X(0)$ into the first column, second column and third column of the matrix $L(s)$ and denote the resulting matrices by $L_1(s)$, $L_2(s)$ and $L_3(s)$ respectively, the quotient from Cramer's rule, we get

$$\mathcal{L}\{x_1(t)\} = \frac{\det(L_1(s))}{\det(L(s))} \tag{8}$$

$$\mathcal{L}\{x_2(t)\} = \frac{\det(L_2(s))}{\det(L(s))} \tag{9}$$

$$\mathcal{L}\{x_3(t)\} = \frac{\det(L_3(s))}{\det(L(s))} \tag{10}$$

Now, from (5) - (10), the Laplace back transform is

$$x_1(t) = \mathcal{L}^{-1}\left\{\frac{k_{01}[(s+(k_{21}+k_{23}))(s+(k_{32}+k_{20})) - k_{23}k_{32}]}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}\right\} \tag{11}$$

$$x_2(t) = \mathcal{L}^{-1}\left\{\frac{k_{01}k_{12}(s+k_{32}+k_{20})}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}\right\} \tag{12}$$

$$x_3(t) = \mathcal{L}^{-1}\left\{\frac{k_{01}k_{12}k_{23}}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}\right\} \tag{13}$$

By applying Heaviside's theorem, from equation (11), (12) and (13) we get.

$$x_1(t) = \frac{k_{01}\{(k_{21}+k_{23}-\lambda_1)(k_{32}+k_{20}-\lambda_1) - k_{23}k_{32}\}}{(\lambda_2-\lambda_1)(\lambda_3-\lambda_1)}e^{-\lambda_1 t}$$
$$+ \frac{k_{01}\{(k_{21}+k_{23}-\lambda_2)(k_{32}+k_{20}-\lambda_2) - k_{23}k_{32}\}}{(\lambda_3-\lambda_2)(\lambda_1-\lambda_2)}e^{-\lambda_2 t}$$
$$+ \frac{k_{01}\{(k_{21}+k_{23}-\lambda_3)(k_{32}+k_{20}-\lambda_3) - k_{23}k_{32}\}}{(\lambda_1-\lambda_3)(\lambda_2-\lambda_3)}e^{-\lambda_3 t} \tag{14}$$

$$x_2(t) = \frac{k_{01}k_{12}(k_{20}+k_{32}-\lambda_1)}{(\lambda_3-\lambda_1)(\lambda_2-\lambda_1)}e^{-\lambda_1 t}$$
$$+ \frac{k_{01}k_{12}(k_{20}+k_{32}-\lambda_2)}{(\lambda_3-\lambda_2)(\lambda_1-\lambda_2)}e^{-\lambda_2 t}$$
$$+ \frac{k_{01}k_{12}(k_{20}+k_{32}-\lambda_3)}{(\lambda_1-\lambda_3)(\lambda_2-\lambda_3)}e^{-\lambda_3 t} \tag{15}$$

$$x_3(t) = \frac{k_{01}k_{12}k_{23}}{(\lambda_3-\lambda_1)(\lambda_2-\lambda_1)}e^{-\lambda_1 t}$$
$$+ \frac{k_{01}k_{12}k_{23}}{(\lambda_3-\lambda_2)(\lambda_3-\lambda_1)}e^{-\lambda_2 t}$$
$$+ \frac{k_{01}k_{12}k_{23}}{(\lambda_1-\lambda_2)(\lambda_1-\lambda_3)}e^{-\lambda_3 t} \tag{16}$$

III. CLINICAL APPLICATION

Table 3.1: Patients Characteristics of the Subjects

Subject	Age (years)	Height (inches)	Weight (kilograms)
C.C.	24	70	72.7
T.F.	26	70	72.7
C.J.	24	71	75
W.S.	28	70	77.3
D.L.	23	75	85.5

*Table 3.2: Experimentally Observed Digoxin Concentrations (ng/ml) by Subjects

| C.C.		T.F.		C.J.		W.S.		D.L.	
Time (min)	Digoxin	**Time (min)**	Digoxin	**Time (min)**	Digoxin	**Time (min)**	Digoxin	**Time (min)**	Digoxin
2.4	21	2.4	22.5	2.1	26.5	2.5	22	2.1	20.5
4.3	22	4.1	21	4.1	21	4.5	18	4.1	17.5
6.2	18	6.2	19	6	18.8	6.1	20.5	6.1	14.5
8.2	15	8.2	18.5	8.1	16.5	8.1	18.5	8.1	12.5
10.2	15.5	10.3	16.8	10.1	14.3	10.1	16.5	10.1	13
14.2	14	14.2	15.8	14.1	14	14.1	16.5	14.1	12
18.2	11.3	18.2	14.5	18.1	13	18.3	11.5	18.1	11
22.2	13.5	22.1	14	22.1	12.3	22.6	13	22.1	9.1
30.1	12.5	30.2	13.3	30	10.3	30.4	9.8	30.1	9.6
45.2	9.1	45.4	9.5	45.1	7.6	45.3	7.3	45.2	5.6
60.2	6.7	61.5	7.3	60.6	5.8	60.2	5.5	60.2	4.9
120.7	3.6	120.1	3.6	120	3.3	121	2.8	120.3	3.2
185.8	2.6	182	2.3	183	2.2	182	2	180.5	2
234.8	2.2	233	1.8	210	1.9	230	1.4	241.8	1.8
355.3	1.2	356	1.2	351	0.52	351	0.73	----	----
485	1.05	467	1.1	469	0.57	480	0.55	470	0.9
944	0.75	943	1.03	-----	-----	924	0.5	948	0.85
1429	1	1465	0.93	1426	0.5	-----	----	1423	0.7
2618	0.54	2119	0.53	2082	0.52	2080	0.4	2187	0.45
2869	0.63	2854	0.44	2833	0.33	2842	0.36	2831	0.43
4306	0.53	4301	0.27	4305	0.24	4320	0.16	4305	0.39

* From [5]
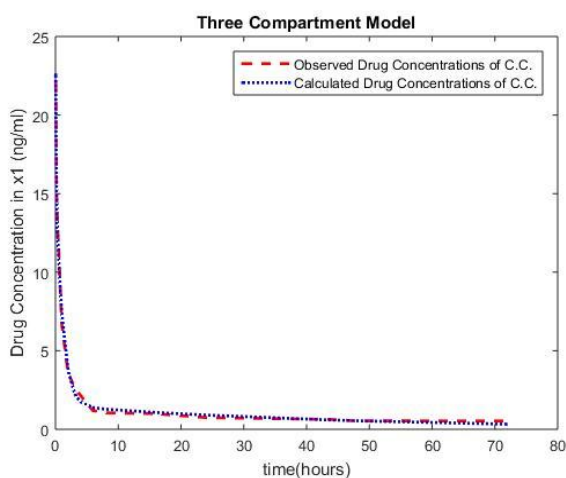
Fig 3.1: Plot of Observed (dashed line) and Calculated Digoxin (dotted line) Concentrations – time profiles of C.C. in three-compartment model.
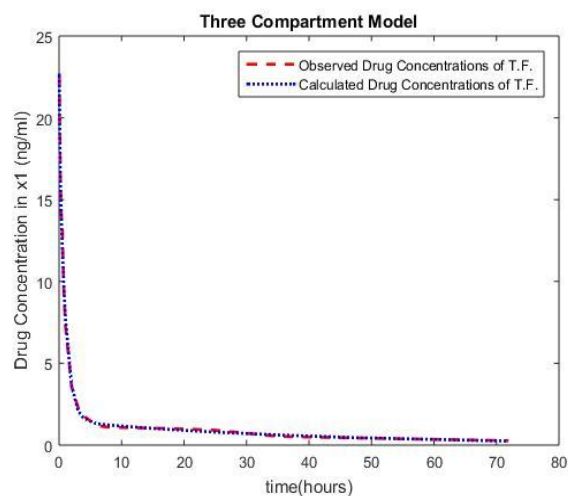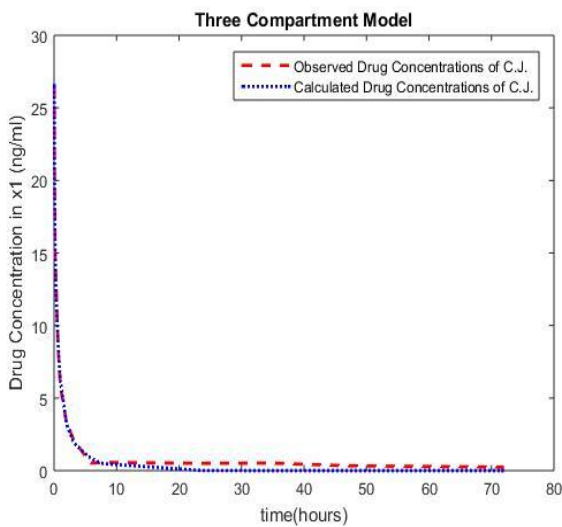

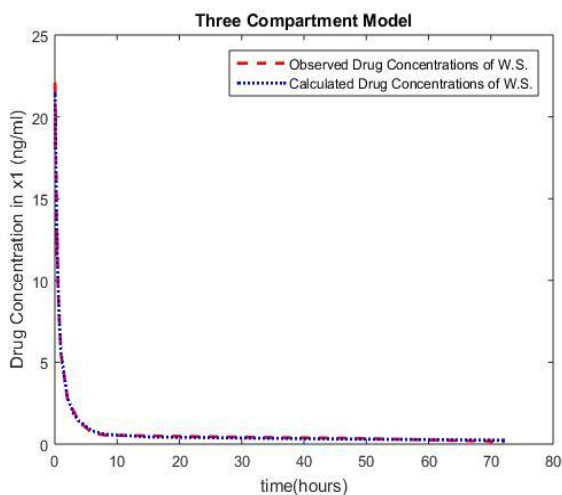**Fig 3.2: Plot of Observed (dashed line) and Calculated (dotted line) Digoxin Concentrations – time profiles of T.F. in three-compartment model**

Fig 3.3: Plot of Observed (dashed line) and Calculated (dotted line) Digoxin Concentrations – time profiles of C.J. in three-compartment model

Fig 3.4: Plot of Observed (dashed line) and Calculated (dotted line) Digoxin Concentrations – time profiles of W.S. in three-compartment model
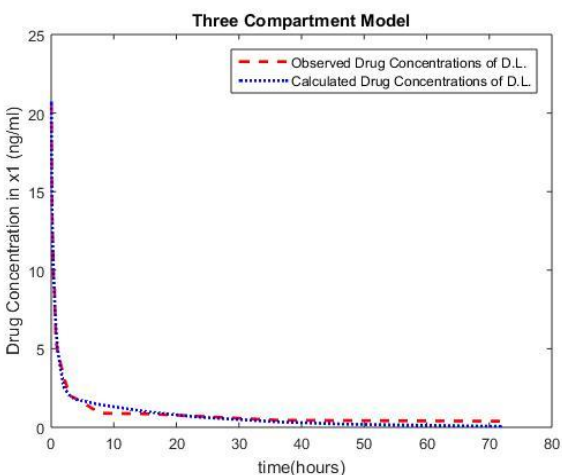

Fig 3.5: Plot of Observed (dashed line) and Calculated (dotted line) Digoxin Concentrations – time profiles of D.L. three-compartment model

Subject	RMSE Values
C.C.	0.4637
T.F.	0.3109
C.J.	0.3765
W.S.	0.333
D.L.	0.3729

Table 3.3: RMSE values of three compartment models of each Subject

Subject Name	k_{12}	k_{21}	k_{23}	k_{32}	k_{30}
C.C.	0.4344	1.2322	0.4993	0.0213	0.0077
T.F.	0.5712	1.1934	0.6654	0.0389	0.1035
C.J.	0.7444	1.2045	0.5923	0.0473	0.0198
W.S.	0.4179	1.7235	0.6432	0.0312	0.0117
D.L.	0.4964	1.3765	0.5723	0.0195	0.0231

Table 3.4: Parameter values of three compartment model of each Subject

IV. CONCLUSION

In this present investigation, we formulated a three compartment model using a coupled ordinary differential equations. The results obtained from our model are coincides with clinical data with RMSE < 0.5 (Table 3.3) which is considered as an efficient model for the data. We observed that our model gives more accurate results for three compartmental model. The solution curves for clinical data and model were drawn using MATLAB and it was observed that the results (Figure 3.1-3.5) were almost coincides. So we can predict serum digoxin concentrations for any given time using our model.

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