Pharmacokinetics of Gentamicin by Intravenous and Intratracheal Administrations

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Abstract **– This paper investigates the pharmacokinetics of a drug delivery system for the purpose of understanding the biodistribution of gentamicin delivered to the blood and tissues by intravenous (IV) and intratracheal (IT) administrations. Numerical solutions for both two-compartment (plasma and tissue) and three-compartment (lung + PFC, plasma, and tissue with IV, IT-Top-fill and IT-Slow fill administrations) models are developed using Euler's method. The drug elimination rate and the rate constants describing the first-order transport between compartments are determined by parameter estimation. The numerical solution is validated against the analytical solution for a two-compartment model with IV injection. The numerical results are statistically compared with the experimental data. It is determined that the IT administration provides efficient drug delivery to the lungs while avoiding the toxicity level in the plasma.**

Keywords – pharmacokinetics; intratracheal (IT) and intravenous (IV) drug administration; Gentamicin, liquid ventilation, Perfluor-chemical (PFC) liquids

I. INTRODUCTION

Pulmonary infection is a major problem prevalent in patients receiving prolonged mechanical ventilation. The infection is often caused by gram-negative bacteria. Effective treatment of gram-negative infection includes aminoglycoside antibiotics. Gentamicin is one such aminoglycoside. Immune response and the endotoxins are released by gram-negative bacteria which causes the alveoli and terminal bronchioles to fill with infectious debris leading to the ventilation and perfusion abnormalities. As a result of this, the conventional IV form of drug delivery is hampered as the drug has to be transported from the blood to the alveoli and finally to the capillaries. Pulmonary administration of aqueous gentamicin is an alternative means of delivering the drug to the lungs.

New born infants receiving prolonged ventilation generally have a pulmonary infection. This infection is often accompanied by acute lung injury, leading to ventilation and perfusion abnormalities. Aerosolization and endotracheal tube delivery are generally used for the effective drug delivery to the pulmonary system. In the presence of irregular pulmonary perfusion, intravenous (IV) delivery of antibiotics to the lung can be less than optimal. Ventilation can be non-uniform and

perfusion may be restricted in the infected regions [1]. These abnormalities hamper conventional intravenous antibiotic therapy because the route of administration proves ineffective in delivering the therapeutic agent to the infected site. Delivery of the drug through circulation is the only other viable route to attack pulmonary infections [2]. Liquid ventilation (LV) is a revolutionary mode for respiratory support. It has also been validated to be an effective alternative means for drug administration. Perfluorochemical (PFC) liquids have a low viscosity and high oxygen and carbon dioxide capabilities [3]. These physical properties of the PFC liquids enable them to improve the mechanics of the lung and gas exchange, and make them advantageous for pulmonary administration of drugs (PAD). The ability of PFC liquid ventilation to improve ventilation and perfusion matching increases the drug exposure to the circulation, thereby achieving the required therapeutic serum drug level [2]. The use of PFCs as adjuncts for intrapulmonary drug delivery has been studied previously; however, the impact of different methods of using neat PFC liquids on the pharmacokinetics on drug delivery has not been evaluated.

There are different parenteral routes for the administration of the drug. The drugs given parentally enter the systemic circulation directly. The main parenteral route for the drug administration is Intravenous (IV) in which the drug is introduced directly into the venous circulation. Pulmonary infection often presents with the ventilation and perfusion abnormalities which can impair intravenous therapy [4]. Intra-tracheal (IT) administration has some obstacles such as an inadequate delivery to affected lung regions and the disruption of the gas exchange associated with it. IT administration of the drug would effectively deliver and distribute the drug to the lung, while maintaining the gas exchange and non-toxic serum levels if administered in a proper way [5]. The IT system is administered in two ways: slow-fill and top-fill. In top-fill administration, the injection of the entire dosage of the drug is done in only one minute. In slow-fill administration, the injection of the entire dosage of the drug is done in a span of fifteen minutes [6].

The primary aim of this research is to develop a good three-compartmental model for the drug administration and to

compare the different parenteral systems for their effective delivery of the drug to the desired parts of the body, namely lung, and plasma and tissues. The three-compartmental model for the drug administration is tested for the three parenteral systems, IV, IT-top-fill and IT-slow-fill, by predicting the concentrations of the drug in the lung, plasma and the tissues with respect to the time after the injection of the drug. The research is then continued to interpret the mass transfer of the drug through the parenteral system while it is being delivered to the various parts such as the lungs, plasma and the tissues.

II.   MATERIALS AND METHODS

A.   In Vivo Experiment

The experimental data used in this paper is from the gentamicin concentrations measured in plasma and organ tissues of anesthetized, mechanically ventilated, newborn lambs who were supported with intratracheal administration of PFC liquid (perflubron LiquiVent®: Alliance Pharmaceutical Corp., San Diego, CA.) and received gentamicin (5 mg/kg) by one of three different methods: 1) intravenously; 2) as a PFC/gentamicin suspension delivered as a bolus following initial intratracheal instillation of the PFC (IT-top-fill); or 3) as a PFC/gentamicin suspension delivered within the initial intratracheal installation of the PFC (IT-slow-fill) [5-6]. Gas exchange, acid-base status and lung mechanics remained within physiological range, independent of the method of administration. The gentamicin dosage of 5 mg/kg was based on clinical guidelines for treating infants. This dosage supports reaching a target drug level of 4-8 μg/ml in the plasma while not exceeding the toxic level of 12 μg/ml over a period of time. This toxic level when attained is dangerous to the cranial nerves in the ears and also to the kidneys. Creatine is a measurement of the kidney function and should generally be less than 1 mg/dL blood. If it exceeds this, it reflects difficulty with excretion. As the value of Creatine is increased, the amount of dosage should decrease accordingly. For example, if a person has a Creatine value of 10, the dosage used for that person should be 10% of that used for a normal person. Generally, for a normal person of 70 kg, the normal dosage of 70 mg/day is used.

B.   Pharmacokinetic models

Pharmacokinetic models have often been used to describe the relationship between the plasma and relevant tissue concentration of the drug over time based on a number of compartments [7, 8, and 9]. The compartmental approach assumes that the drug is delivered into compartments in the body that usually represent body fluids, or a particular region, an organ, a group of tissues in the body. The drug is assumed to be uniformly distributed in the compartment. The uniform or spatial distribution of the drug with in the body is accomplished by having a number of compartments with in the body. This assumption of having a uniformly distributed drug with in the body is valid as the cardiac output in humans is normally 5mL/min and the blood volume is 5L, giving an effective residence time of 1 minute per passage through the circulation system. Thus, as the drug distribution is carried out in the span of hours and the body's fluids have a flow rate in minutes, the assumption stands valid. The drug movement between the compartments is generally described by a simple irreversible or reversible first-order rate process [10].

B-1.   Two-Compartmental Model with IV Injection

This model consists of two compartments, a central compartment and a tissue or peripheral compartment. The central compartment consists of blood, extra cellular fluid and highly perfused tissues. The tissue or peripheral compartment contains the tissues where the drug perfuses slowly. Drug transfer between the two compartments is assumed to take place by first order processes. Thus, the plasma level-time curve for a drug that follows a two compartment model shows that the plasma level concentration decreases biexponentially as the sum of two first order processes – distribution and elimination unlike a plasma level-time curve of a the single intravenous dose that does not decline as a single exponential process.

Fig. 1 shows the two compartment model with IV injection. The drug does not rapidly equilibrate as in one compartment model. The rate constants K_{pt} and K_{tp} represent the first order transfer constants for the movement of the drug from the plasma compartment to tissue compartment (K_{pt}) and from the tissue compartment to plasma compartment (K_{tp}). The rate constant K_e represents the first order transfer constant for the excretion of the drug from the central compartment.

Unsteady mass-balance equations for the plasma compartment and tissue compartment are given by

$$V_p \frac{dC_p}{dt} = K_{tp}V_tC_t - (K_e + K_{pt})V_pC_P \qquad (1)$$

$$V_t \frac{dC_t}{dt} = K_{pt}V_pC_p - K_{tp}V_tC_t \qquad (2)$$

where V_p and V_t represent the apparent volume distributions of the plasma and tissue compartments. C_p and C_t represent the concentrations with in these respective compartments. The initial condition for this two compartment IV injection model is that at time $t = 0$, the tissue concentration is zero as the drug is not present in any of the tissues and the plasma
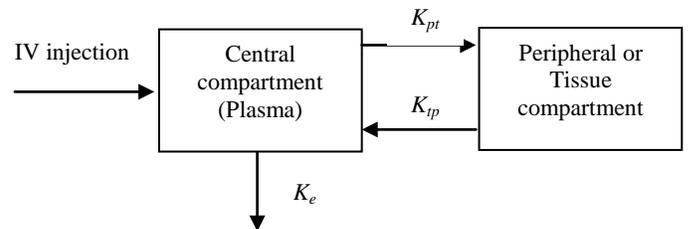

Figure 1: Two-compartment open model with IV injection.

concentration is given by the ratio of the drug dose (*D*) and the apparent distribution volume of the plasma compartment. Thus, at $t = 0$, $C_t = 0$ and $C_p = D/V_p$. These initial conditions can be used to solve the above equations for the concentrations of the compartments as a function of time using Laplace transforms. Thus,

$$C_p(t) = \frac{D}{V_p(A-B)}[(K_{tp} - B)e^{-B \cdot t} - (K_{tp} - A)e^{-A \cdot t}] \qquad (3)$$

$$C_t(t) = \frac{DK_{pt}}{V_t(A-B)}[e^{-B \cdot t} - e^{-A \cdot t}] \qquad (4)$$

where A and B are first order rate constants.

$$A = \frac{1}{2}\{(K_{pt} + K_{tp} + K_e) + [(K_{pt} + K_{tp} + K_e)^2 - 4K_{tp}K_e]^{1/2}\} \qquad (5)$$

$$B = \frac{1}{2}\{(K_{pt} + K_{tp} + K_e) - [(K_{pt} + K_{tp} + K_e)^2 - 4K_{tp}K_e]^{1/2}\} \qquad (6)$$

B-2. Three-Compartment Open Model with IV Injection

This model is an extension as well as a refinement of the two compartment model. The central compartment is divided into a lung compartment which includes PFC, and a plasma compartment. IV injection of the drug is done into the plasma compartment. The drug then travels to and fro from the plasma compartment into the lung and tissue compartments. The drug is finally delivered into the kidney from where it is eliminated. Drug transfer between the compartments is assumed to take place by first order processes.
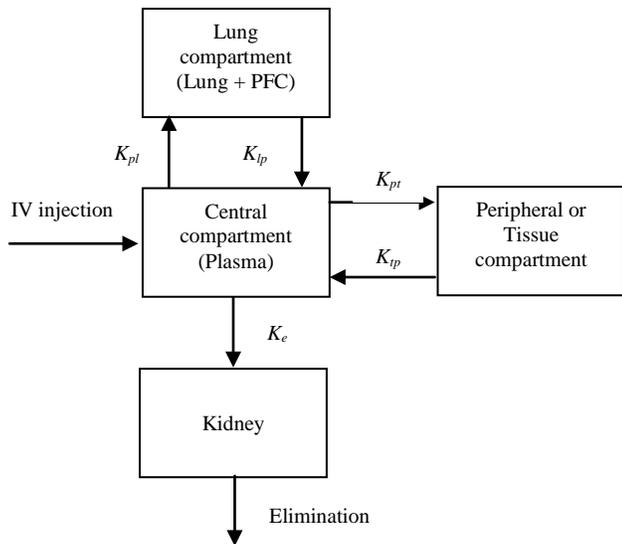
Fig. 2 shows the three compartment model with IV injection. The drug takes more time to equilibrate compared to the two compartment model. The rate constants K_{pt}, K_{tp}, K_{pl} and K_{lp} represent the first order transfer constants for the movement of the drug from plasma to tissue, tissue to plasma, plasma to lung, and lung to plasma, respectively. The rate constant K_e represents the first order transfer constant for the elimination of the drug from the central compartment to the kidneys from when it is excreted.

Unsteady mass balance equations for the plasma, the lung, and the tissue compartments are given by

$$V_p \frac{dC_p}{dt} = K_{lp}V_{lung}(C_{lung} - C_p) + K_{tp}V_t(C_t - C_p) - K_e V_p C_P \qquad (7)$$

$$V_{lung} \frac{dC_{lung}}{dt} = K_{lp}V_{lung}(C_p - C_{lung}) \qquad (8)$$

$$V_t \frac{dC_t}{dt} = K_{tp}V_t(C_p - C_t) \qquad (9)$$

where V_p, V_{lung} and V_t represent the apparent volume distributions of the plasma, lung + PFC and tissue compartments respectively. C_p, C_{lung} and C_t represent the concentrations with in these respective compartments. The initial condition for this two compartment IV injection model is that at time t = 0, the concentration of the drug in the tissue and the lung is zero as the drug is not present in any of the tissues and lung at the time of injection of the drug in the body and the plasma concentration is given by the ratio of the drug dose (D) and the apparent distribution volume of the plasma compartment. Thus, at $t = 0$, $C_t = 0$, $C_{lung} = 0$ and $C_p = D/V_p$.

B-3. Three-Compartment Open Model with IT

Fig. 3 shows the three compartment model with IT injection. The rate equations are the same as Eqs. (7-9) except the initial condition at $t = 0$, $C_t = 0$, $C_p = 0$ and $C_{lung} = D/V_{lung}$.

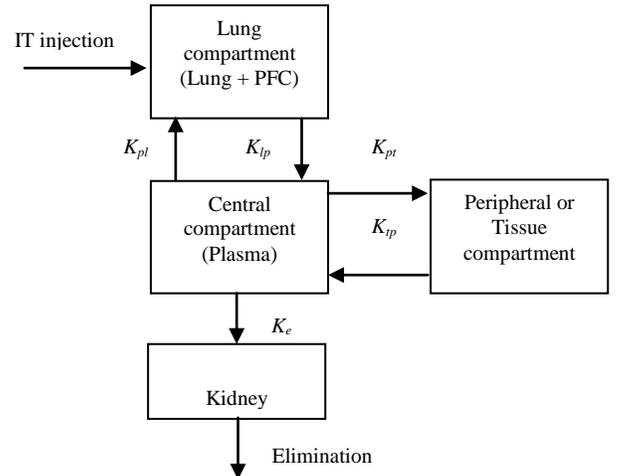*Figure 2: Three-compartment open model with IV injection.*

Figure 3: Three-compartment open model with IT injection.

There are two types of IT injection models based on the type of injection of the drug into the lung. If the drug is injected at an instant, then the type of injection is called Top-fill administration and if the drug is injected slowly in a span of 15 to 30 min, it is called Slow-fill administration. The slow fill administration is modeled in two ways. In one of the cases, the rate of transport of the drug from the lung to the plasma compartments is taken as half of the top-fill administration. In this case, there would be no change in the equations that guard the process. In the second case, we assume the drug, in this case gentamicin, is injected in to the lung along with the PFC in a span of fifteen minutes. In this case, the equation of the lung compartment changes for the first fifteen minutes, which is given by

$$V_{lung}\frac{dC_{lung}}{dt} = K_{lp}V_{lung}(C_p - C_{lung}) + (Dosage/15) \qquad (10)$$

III.   RESULTS AND DISCUSSIONS

First, the numerical model is validated using the two-compartment model with IV injection. The results will then be presented using the three-compartment model, which illustrates the time history of the drug concentration in the lung, the plasma, and the tissue.

A.   Validation of Numerical Solution with Analytical Solution for Two-compartment Model with IV Injection

Figure 4 shows the comparison of the drug concentrations in the plasma and tissue over a span of 4hrs for the two-compartment pharmacokinetic model with IV injection. The Euler method with a time step of 1 min was used for the numerical analysis, yielding an excellent agreement between the numerical solution (red circles) and analytical solution (blue line, Eqs. 3-6). Decreasing the time step has very little effect on the numerical results. Therefore, a time step of 1 min is used for all numerical models in this paper.
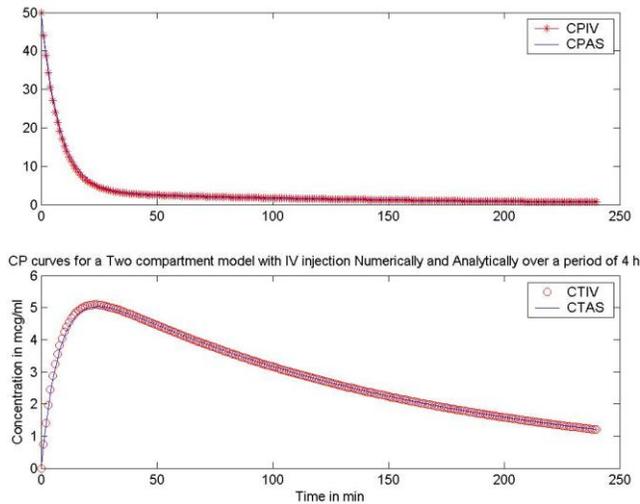
B.   Numerical Solutions(MATLAB) for the IV, IT-Top-fill, and IT-Slow-fill administrations of the Drug (Three-Compartment Model)

A detailed sensitivity analysis is performed by varying the lung volume, plasma volume, and tissue volume as well as the rate constants, K_e, K_{lp} and K_{tp} [11]. This allows us to best estimate the values used in the numerical analysis. To satisfy the steady state conditions for mass transfer, the equilibrium equation of $V_1K_{12} = V_2K_{21}$ between any two compartments is assumed. The following data are used for the program:

Drug dosage = 5 mg/kg.
Volume of lung = 25 ml/kg.
Volume of the PFC = 20 ml/kg.
Volume of the plasma = 100 ml/kg.
Volume of the tissues = 400 ml/kg.
Lung to plasma for Top-fill and IV, $K_{lp} = 0.011$ min^{-1}.
Lung to plasma for Slow fill, $K_{lpsf} = K_{lp}/2 = 0.005$ min^{-1}
Rate constant from tissues to plasma, $K_{tp} = 0.015$ min^{-1}
Elimination rate constant, $K_e = 0.693/t_{1/2} = 0.05775$ min^{-1}

Figure 5 describes the concentration of the plasma, C_P, obtained from the numerical solution for the IV (CPIV), Top-fill IT (CPTF) and Slow fill IT (CPSF) administrations over a span of 4 hours. The curves for the top-fill and the slow fill are zoomed in separately to show the absorption phase (increasing drug concentration) and the elimination phase (decreasing drug concentration) of the drug distribution. The maximum values for the plasma concentrations occur after 30 min in case of top-fill administration and after 68 min in case of slow fill administration.

Figure 6 describes the plasma, lung and tissue oncentrations for IV administration over a span of 4 hours. The C_t and C_{lung} values for the IV administration are similar to those for the IT administration (Fig. 5). However, the C_p level is much lower in the IT administration (below 4 μg/ml) than the C_p level (close to 50 μg/ml at t = 0) in the IV administration so that the IT has the benefit of avoiding the toxicity level in the plasma.

Figure 4: Validation of plasma and tissue concentrations for a two-compartment model with IV injection (mcg = μg).
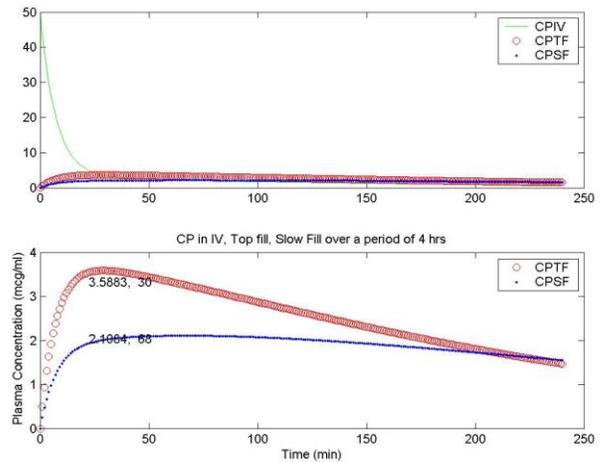

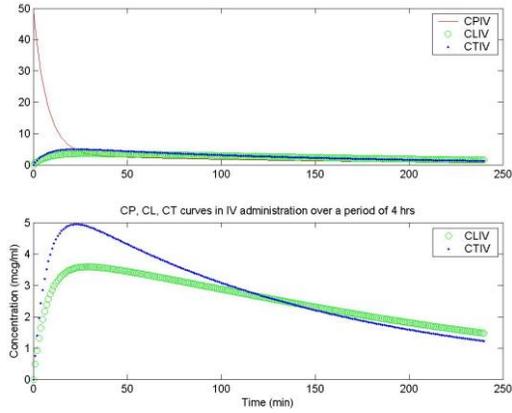Figure 5: C_p curves for IV, IT Top-fill, IT Slow-fill over a period of 4 hrs (mcg = μg).

Figure 6: C_p (red), C_{lung} (green), C_t (blue) curves in IV administration (mcg = µg).

C. Comparison of the Plasma Concentrations for the Model and the Experiments

Figure 7 shows the comparison of the plasma concentrations predicted by the model and the experiment [1] for a span of 4 hrs using the IT-Top-fill administration. The figure shows that the data from the model agree with the experimental values within the measurement uncertainties. The data are analyzed statistically by a two sample test with a p value of 0.9496. The p value is much greater than 0.05, showing that the model predicts the experimental data quite well. The error bars for the data are obtained with a 95% confidence level.

Figure 8 shows the comparison of the plasma concentrations from the model and the experiment for a span of 4hrs using the IT-Slow fill administration. The figure shows that the data from the model predicts the same way until the elimination of the drug started when compared with the experimental values. The data are analyzed statistically by a two sample test with a p value of 0.6961 (>> 0.05). The plasma drug concentrations predicted by the numerical model

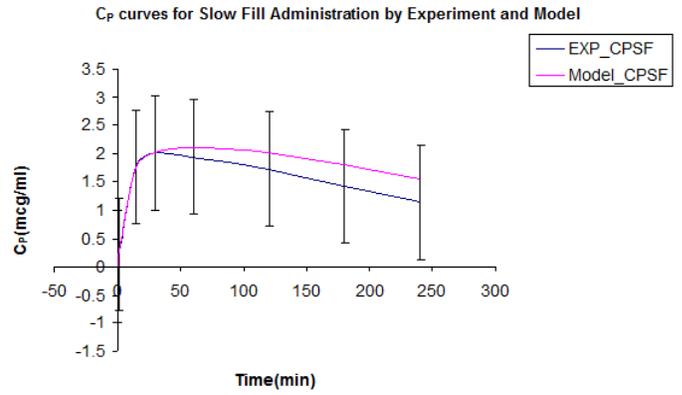*Figure 8: C_p curves for Slow Fill Administration by Experiment and Model for varying K_{lp} for the first 15 minutes (mcg = µg).*

are within the experimental errors (95% confidence level). The large error bars in Figs. 7 and 8 are caused by our animal models [1-2] which were at the earlier stages of development where there was intrinsic biological variability in ventilation, distribution of ventilation, pulmonary blood flow and the distribution of the pulmonary blood.

Figure 9 shows the comparison of the plasma concentrations from the model and the experiment for a span of 4 hrs using the IV administration. The figure shows that the data from the model are in good agreement with the experimental data until the elimination of the drug started at t = 20 min, when the model under predicts the C_p values during the elimination phase of the drug. The error bars for the data were obtained with a 95% confidence level.

The elimination half-life of gentamicin in the plasma is estimated to be 0.2 hrs (Fig. 4). The above values can be used to estimate the half-life of gentamicin in the whole body to be about 150 mins (Figs. 6, 7, 8) after the administration of the gentamicin in all the models which validates the previous research performed on gentamicin [7]. The half-life of 0.2 hrs
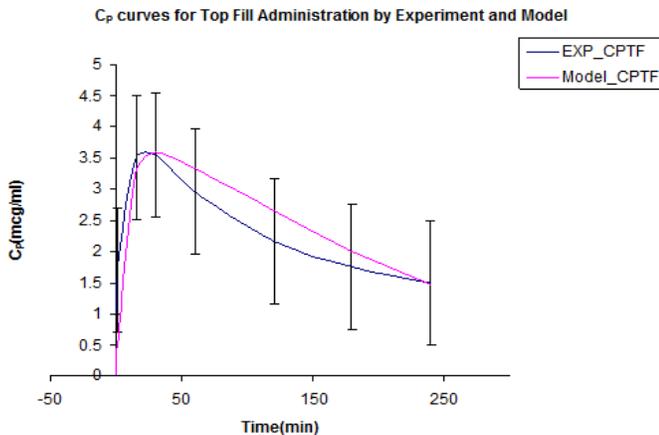

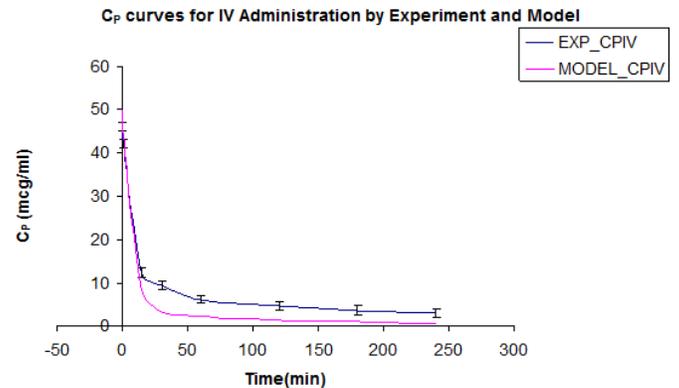*Figure 7: C_p curves for Top-fill Administration by Experiment and Model*

Figure 9: C_p curves for IV Administration by Experiment (blue) and Model (red)

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in the plasma compartment may have been underestimated in Fig. 9, leading to a faster drug elimination than the experimental data. A sensitivity analysis of $t_{1/2}$ (0.2, 0.4, 0.6 and 0.8 hrs) for IT top-fill administration is analyzed. Figure 10 shows that as $t_{1/2}$ increases, the maximum value of the plasma concentration is also increased. It can also be seen that at the end of the elimination phase, a small amount of drug is left in the plasma when the half life time was 0.2 hrs. By comparing the C_p values from Fig. 9 with the experimental C_p value at t = 4 hrs (Fig. 8), 0.2 hrs was chosen to best predict the IT drug delivery. The IT drug delivery is more effective than the IV drug delivery for treating lung infections [1,2,5,6]. More detailed sensitivity analysis was given in [11].

CONCLUSION

The numerical analysis using Euler's method programmed with MATLAB gives good agreement with earlier experimental data for IV administration, IT top-fill administration, and IT slow fill administrations. The drug transfer rate coefficients are estimated from the data obtained from the earlier studies performed on newborn sheep [5-6]. Various parameters such as the volume of the lung along with the PFC, volume of the plasma compartment, volume of tissue compartment, transport rate of the drug from the lung to the plasma, transport rate of the drug from the tissues to the plasma, elimination rate from the plasma were investigated.

The analytical and numerical solutions for the two compartment model show good agreement with each other. The transfer rate of gentamicin from lung compartment to the plasma compartment is estimated to be 0.011 min^{-1}. The transfer rate of gentamicin from tissue compartment to the plasma compartment is estimated to be 0.015 min^{-1}. The elimination half-life of gentamicin is estimated from the two compartment model to be 0.2 hrs. The pharmacokinetics of gentamicin by IV administration, IT top-fill administration and IT slow-fill administration are compared. The half-life of
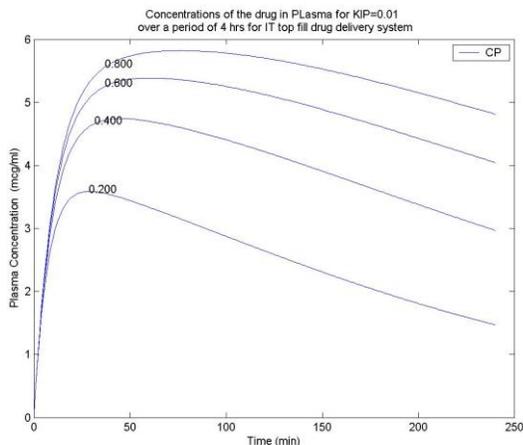
gentamicin in the whole body (Figs. 4-8) is found to be about 150 min, which agrees well with data in the literature [7].

The results obtained from the model for the three compartment IV administration and IT top-fill administration are within the experimental errors when compared with the earlier experimental data. The dosage sensitivity of the gentamicin is calculated for the IT top-fill administration and the IV administration. It is clearly visible that the same amount of the dosage yields a higher dosage of the gentamicin to the lung and lower dosage to the plasma by the IT top-fill administration than the IV administration. This is very helpful in case of an injured lung affected by Pneumonia. The required target levels of 4 to 8 $\mu g/ml$ of drug are achieved by all the administrations over a length of time. The model was also built to avoid the toxic level of the drug all the time.

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Figure 10: Sensitivity Analysis of half-life of the drug in the plasma for IT top-fill administration (mcg = μg).