International Journal of Scientific Engineering and Research (IJSER)
ISSN (Online): 2347-3878
Index Copernicus Value (2015): 62.86 | Impact Factor (2015): 3.791

Modeling of Physiology Based Toxico-Kinetics and Toxico-Dynamic to Diagnose Acute Effects of Nicotine on Heart Rate

Chandiyauma S[1], Helen R[2]

[1]Departmen of EEE (Student), Thiagarajar College of Engineering, Madurai

[2]Department of EEE (Faculty), Thiagarajar College of Engineering, Madurai

Abstract: ***In the modern world persons addicting to drugs are increasing gradually. Drugs are mostly in the form of cocaine, nicotine etc. which are harmful to our human body. The most commonly affected organs are lung, liver, kidney. In this paper we analyzed the effect of nicotine in lung, liver and kidney using Physiologically Based Toxico-Kinetics and Physiologically Based Toxico-Dynamics modeling. The effect of nicotine is more in lungs which also affect blood concentration and heart rate of the human. We also analyzed the efficiency of lung assist device by placing compliance chamber in between heart and lung. By using compliance chamber we can able to maintain the pulmonary artery pressure in the range of 8 to 25mm/Hg.***

Keywords: Physiologically Based Toxico-Kinetics (PBTK), Physiologically Based Toxico-Dynamics (PBTD), artificial lungs, lung transplantation, compliance chamber (keywords)

1. Introduction

Tobacco which is particularly smoked product has been associated with great harm and growing public disapproval and can be expected to suffer in the market place. This situation has created opportunities for other less harmful nicotine containing products causes immediate effect on cardio vascular disorders and delayed effect on respiratory and cancer disorders [1]. The straw nicotine oral delivery system is a novel form of nicotine replacement theraphy designed to provide not only nicotine but also oral and manual stimulation and ease of dosing. The straw is the single-use. Drinking straw containing loose nicotine bitartrate particles that are ingested with the first sip of beverage . Straw may be a useful new tool in supporting smoking cessation for several reasons [2]. The absorption of nicotine delivered by a transdermal delivery system (tedious) was investigated in two separate studies, single dose proportionality study and multiple dose study. The Area Under Curve (AUC) and Maximum Concentration (Cmax) values are proportional to the dose. Transdermal delivery provides continuous absorption of drug through stratum corneum even during sleep [3]. Sympathetic over activity is implicated in the increased cardiovascular risk of cigarette smokers.

Excitatory nicotine receptors are present on peripheral chemoreceptor. Chemoreceptors located in the carotid and aortic bodies increase Ventilation (Ve), Blood Pressure (BP), Heart Rate (HR) and Sympathetic Nerve Activity to Muscle circulation (MSNA) in response to hypoxia. Nicotine Replacement Technique (NRT) increases myocardial oxygen consumption in periods of reduced oxygen availability [4]. The Pharmaco-Kinetic and Hemo-Dynamic effects of nicotine patch are significantly different between smokers and non-smokers. The Hemodynamic effects of the nicotine patch on blood pressure and heart rate were greater in nonsmokers than in smokers, and the parasympathetic effects such as nausea and vomiting occurs more frequently in non-smokers than in smokers [5].

The physiologically based Toxico-Kinetic model treats the time course of chemical distribution. It is illuminating to use fugacity to directly examine the relative equilibrium status of compartments and to provide the direct estimate of chemical activity thus with suitable parameterization it has potential for both bio-concentration and toxicity expressed as median lethal concentrations, critical body residues, and chemical activity as a function of time to death[6]. The Physiologically Based Toxico-Kinetics (PBTK) and Toxico-Dynamic modeling (PBTD) was applied to provide concentration time profiles of nicotine. This model is used to estimate the heart rate in terms of maximum concentration based on inhalation, oral intake and absorption. The Toxico-Dynamic model is used to analysis the effect of nicotine in heart rate and the Toxico-Kinetic model is used to analyze the effect of nicotine in different organs of our body (kidney, liver, lung). Lungs are mainly affected during smoking [7].

Table 1: nicotine dosage

Types	Dosage level
Cigarettes(1.2mg) 3 per day 8 per day 14 per day 21 per day	 3.6mg 9.6mg 16.8mg 25.2mg
Dermal patches	7mg 14mg 21mg
Nicotine lozenges 2mg for every 2 h 2mg for every 1h 4mg for every 1h	 24mg 48mg 96mg

Artificial lungs may serve as transplant alternatives to patient with respiratory failure. To provide the pulmonary replacement, the device cannot significantly alter right ventricular after load. Addition of a compliance chamber reduces pulse wave reflection and normalizes ventricular function. The pulmonary replacement with the low-resistance artificial lung is tolerated by the right ventricular in this short term model [8]. Matching the impedance of an artificial lung for pulmonary replacement to native pulmonary impedance is important in preventing right ventricular dysfunction. The lunged parameter model and the bench top simulation will aid in the design and testing of compliance chamber modification to improve its efficiency [9]. The contribution of this paper gives the detailed analysis of changes in blood concentration according to the nicotine dosages in liver and kidney using Physiologically Base Toxico-Kinetics (PBTK) modeling and heart rate changes based on using Physiologically Based Toxico-Dynamic modeling (PBTD) and cardiac output is determined. Based on this changes the lung is mainly affected which is demonstrated in relation between heart rate, cardiac output and blood flow. As a result of fixing artificial lungs that is, assisting device for lungs which is replaced instead of original lungs .Every device has certain original efficiency. Inorder to increase its efficiency, a compliance chamber is designed and fixed.

2. Nicotine Dosage Used

The dosages were selected for resting condition to show the difference in heart rate changes, blood concentration and cardiac output at identical concentration levels of nicotine. The selected dosing conditions for nicotine with web and literature references are mentioned in Table 1.

3. Physiological Modeling

A) Physiologically Based Toxico-Kinetic modeling (PBTK)

In this model the drug concentration profile result from the uptake and elimination capacity of organ composing the body, the distribution of the drug to an organ depends on the blood flow to the organ, the organ weight and the partition coefficient of the drug between the blood and the organ, the major distribution takes place in liver,GI tract and kidney. The block representation of the PBTK model is represented in Figure 1.

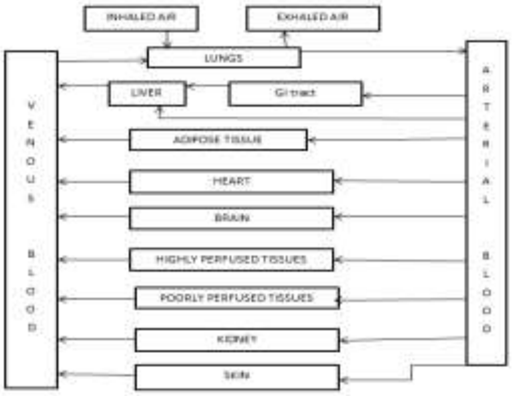

Figure 1: PBTK flow chart

Liver and GI tract:
The model equations for the liver and GI tract are given

liver:

$$\frac{dAliv}{dt} = Flgit + FORMliv + Fliv.\left(Cart - \frac{Cliv}{PCliv}\right) - METliv \quad \textbf{(1)}$$

$$Cliv = \frac{Aliv}{Vliv} \quad \textit{(2)}$$

GI tract:

$$Flgit = fra.fgit.\frac{Cstm}{PCgit} + frb.fgit.\frac{Csi}{PCgit} + frc.fgit.\frac{Cli}{PCgit} \quad \textbf{(3)}$$

$$Cstm = \frac{Astm}{Vstm} \;;$$

$$Csi = \frac{Asi}{\left(\frac{3}{4}\right)Vint} \;;$$

$$Cli = \frac{Ali}{\left(\frac{1}{4}\right)Vint} \quad \textbf{(4)}$$

Where:
Aliv = amount of nicotine present in liver.
Fliv = fraction of liver.
Cart = concentration present in arteries.
PCli = partial coefficient of liver.
METliv = metabolism of nicotine in liver.
Flgit= GI tract formation.
Fra, frb, frc = absorbed fractions that reach liver from stomach, small intestine & large intestine.
Fgit= fraction of GI tract.
PCgit = Partial Coefficient of GI tract.
Cstm = Concentration of nicotine present in stomach.
Csi= Concentration of nicotine present in small intestine.
Cli =Concentration of nicotine present in large intestine.
Astm, Asi, Ali = amount of nicotine present in stomach, small intestine & large intestine.
Vstm =volume of stomach.
Vint = volume of intestine

Table 2: Parameters of TK model

Parameters	Values
Fliv	0.254
Fgit	0.025(man) 0.0265(woman)
Fra	0.2
Frb	0.6
Frc	0.2
PCgit	0.81
Cstm	Varies
Csi	Varies
Cli	Varies
Cart	0.8
FORMliv	0
Cliv	0.0061
PCliv	0.81
METliv	0.1674

Table 3: weight of organs

Organs Name	*% of Body Weight*
Stomach	0.21
Small intestine	0.91
Large intestine	0.53
GI	1.71
Kidney	0.44
Heart	0.47
Lungs	0.76

These parameters values are mentioned in M.Gajewska et al.,[8] and Loizou et al.,[16] which are discussed in the references. The volume of the organ is calculated with the information of organ's weight and its density is tabulated below. This is specified as the standard values for the average body weight of 70 kg. These data are taken from the paper (physiological parameter values for physiologically based pharmacokinetics models published by Brown et al.,)

Kidney

The equation for the kidney is given as

$$\frac{dAkid}{dt} = Fkid\left(Cart - \frac{Ckid}{PCkid}\right) - CLR\left(\frac{Ckid}{PCkid}\right).$$

$$Ckid = \left(\frac{Akid}{Vkid}\right) \quad \textbf{(5)}$$

Where:
Akid= amount of nicotine present in kidney
Fkid = blood flow rate through kidney
Ckid = concentration of nicotine

The standard values of kidney parameters are mentioned by M.Gajewska et al.,in his paper[3].Thus from the above information the modeling of kidney is done and the amount of changes in blood concentration for each organ is evaluated, based on the value of nicotine dosage given into our body, the amount of nicotine that can be distributed to the organ can be estimated.

B) Physiologically Based Toxico-Dynamic modeling (PBTD):

The PBTD model explanation is outlined in fattinger et al., [7]. Here venous blood concentration plays a vital role. Using PBTD the model for heart rate was developed. Here modification is necessary for the case of nicotine affected during exercise only. The block diagram for PBTD model is given in Figure 2.

Table 4: Parameters value for kidney

Parameters	Values
Fkid	0.19 (woman) 0.2 (man)
Akid	Varies
PCkid	1.34
Cart	0.8
CLR	0.036

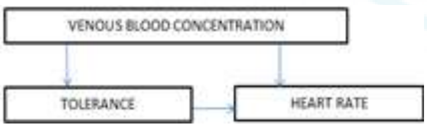

Figure 2: PBTD model

The above block diagram gives the better fit and better description for the pharmacological response. Here for avoiding some issues one assumption is taken that the chemical concentration in blood(Cven) is always much less than the concentration needed to produce half of the maximal effect(Cven,50) (ie) Cven<<<<Cven,50. The antogonist formation and elimination rates are assumed to be contant and are dependent on venous blood concentration. The equation for the PBTD model is given as.

$$E = E0 + \frac{\left(\frac{Emax}{Cven}\right).C^{y}ven}{\left(1+\frac{c^{y}ant}{C^{y}ant,50}\right)\left(1+\frac{c^{y}ven}{c^{y}ven,50}\right)} \quad \textbf{(6)}$$

$$E = E0 + \frac{(s).C^{y}ven}{\left(1+\frac{c^{y}ant}{C^{y}ant,50}\right)} \quad \textbf{(7)}$$

$$Vven.\left(\frac{dCant}{dt}\right) = Ka,ant.(fu.Cven) - Kel,ant.Cant \quad \textbf{(8)}$$

Where:
Ven = Venous blood
Cant = Concentration of antagonist
Ka,ant; Kel,ant = Formation and elimination rates of antagonist
Fu = Free fraction of a stimulant
E = Effect on heart rate
E0 = Base line effect
Emax = Maximal effect
S = Ratio of Emax
Cven = venous blood concentration

Parameters Used:

The parameter used are mentioned by porchet et al., in his paper[20]. Thus from the above information the modeling is done and the amount of changes in heart rate is determined, based on the value of nicotine dosage given into our body, the amount of nicotine that can be distributed also be found out.

These two modeling are used only for analyzing purposes. Thus the acute effect of nicotine in each organ and heart rate can be determined using this modeling.

C) Relation Equation

The heart rate and the blood flow both are indirectly related. During inspiration the lungs will expand and during expiration process the lungs will contract. Consequently in heart during inspiration there will be increase in heart rate and during expiration there will be decrease in heart rate. During intake of nicotine mostly the ventricle of the heart is affected. Hence ventricular assisting device (VAD) is used .The output from the VAD is given to the lungs and hence the input to the lungs depends on the output from the VAD (ie) ventricle of heart. The following equation gives the relation between heart rate and pressure.

$$P=SV*HR*TPR \quad \textbf{(9)}$$

$$BF=P/R \quad \textbf{(10)}$$

Table 5: Parameters of PBTD model

Parameters	*Values*
Cven	Varies
Eo	61.2,64(at rest) 145(during exercise)
S	1000
Ka,ant	3
Kel,ant	6
Cant,50	0.00772
Y	1(rest) 0.6 (during exercise)

Where
P = Pressure
SV = Stroke Volume
HR = Heart Rate
TP =Total Pressure Resistance
R =Resistance
BF =Blood Flow

The cardiac output (Q) is termed as the total volume of blood being pumped from heart ventricle in minute (ie) blood leaves from the left ventricle every minute. At average resting time the cardiac output will be 5L/min and during exercise time it will be 4-7 times higher than rest.

$$CO=SV*HR \quad \textbf{(11)}$$

The stroke volume (SV) is defined as the volume of blood ejected from heart ventricle with each beat.at average resting time the stroke volume will be 60-70ml/beat. The heart rate (HR) determines the number of times heart pumps in 1 minute. At average resting time the heart rate will be 60-100 bpm (beats per minute).

4. Design of Compliance Chamber

In general compliance means Ability of hollow organ to distend and increase volume with increasing trans-mural pressure to resist coil towards original dimensions on application of a distending or compressing force. It is also recognized as the tendency of arteries and veins to stretch in response to pressure has a large effect on perfusion and blood pressure. It is represented as $C=\Delta V/\Delta P$.
Where

C= compliance
ΔV= change in volume
ΔP= change in pressure

Here three element lumped parameter model is used to implement compliance chamber. The circuit consist of compliance element (C*) and the resistive elements (R1*, R2*) before and after the C*

The design of compliance chamber is outlined by the following equations

$$P^*=(R1^* + R2^*)Qref \quad \textbf{(12)}$$
$$Q^*=Qref\ Q \quad \textbf{(13)}$$
$$Ri^*=(R1^*+R2^*)Ri \quad \textbf{(14)}$$
$$T^*=Tpulse^*t \quad \textbf{(15)}$$

Where:
P*= pressure across the compliance element.
Tpulse= period of pulsatie flow.
T=ratio of the time scale of oscillatory flow.
R=total resistance in compliance chamber.
Qref=maximum value of periodic inlet flow
Q1= flow of blood in cardiac output.
Q2= flow of blood in pulmonary vein.
P1= pulmonary artery pressure.
P2= Left auricle pressure (10 mm/hg)

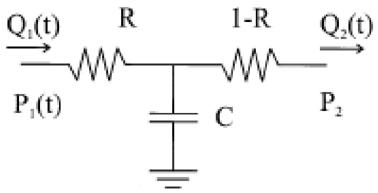

Figure 3: Compliance Chamber

From this the right ventricle pressure which is to be given for lungs as input is determined. which should have the range from 9mm/Hg to 21 mm/Hg.

5. Heart-Lung Block

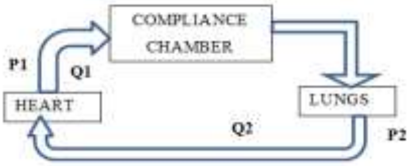

Figure 4: Heart-Lung model

The lung plays a major role in respiration; the purification of blood process is carried out in the lungs. The respiratory model for the human lungs is more complex. When there is the problem in lungs most of people undergoes, lung transplantation. But this process will get succeeded only when both the donor and receptor requirements matches. Hence the next developed system is fixing an artificial lung that is the assisting device which do all the work instead of lungs. The right side of a human heart play an important role, it's function is to collect a blood that contain oxygen and carbon dioxide from the body and transfer it to the lungs which collect all the oxygen and releases carbon dioxide. Now the left side of the heart collects bloods that contain a lot of oxygen from the lungs and then transfer it to the different part of the body.

The model for the combination of heart and lung is done in which the cardiac output is evaluated. The equation for all of the elements are then combined using continuity and the requirement that the total pressure drop along the circuit equal p1-p2. The non-dimensional governing equation of the system is given as

$$\frac{dP1(t)}{dt} = -T\frac{P1(t)}{1-R} + TQ1(t)(1 + \frac{R}{1-R} + R\frac{dQ1(t)}{dt} \quad \textbf{(16)}$$

$$Q2 = Q1 - T\frac{dP1}{dt} + (\frac{R}{T})\frac{dQ1}{dt} \quad \textbf{(17)}$$

where:
P1 = pulmonary artery pressure
Q1= flow of cardiac output
P2 =left atrial pressure (10mm/Hg)
Q2 = flow in pulmonary vein
T = time period

From this the pressure of heart P1 is determined for every change in the cardiac output. This is given as the input to the compliance chamber and the assisting device.

6. Result and Discussion

Analysis

Analysis for liver and kidney using PBTK modeling:

Based on the PBTK modeling which is represented in the equations (1)(2)(3)(4) and Figure 1 the simulation is performed in MATLAB that is given in figure 8,9 the analysis is carried out. The analysis is done in order to find out the impact of nicotine in blood concentration of different organs (liver and kidney). The graphical representation of analysis shown in Figure 6, the X-axis represents the types of dosages and the y-axis represents the blood concentration values of both liver and kidney. It clearly conveys that while increasing the dosage level the blood concentration increases and the impact of nicotine is more in kidney than in liver but while comparing with lungs the impact is greater in lungs.

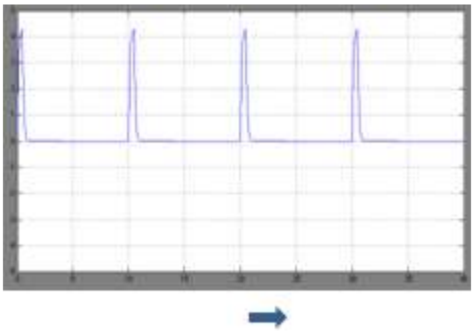

Figure 5: Right Ventricular Pressure (P1)

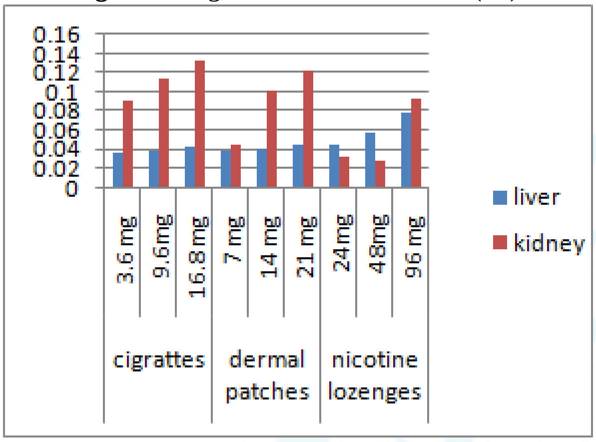

Figure 6: Blood concentration analyses

Analysis of heart rate using PBTD modeling

Based on PBTD modeling represented in the equations (6),(7),(8) and figure 2 the simulation is performed and given in figure10 and the analysis is done. This analysis is to identify the heart rate changes. The graphical representation of analysis is outlined in figure 7 where the x-axis represents the dosages and the y-axis represents the heart rate while increasing the dosage level the heart rate also increased.

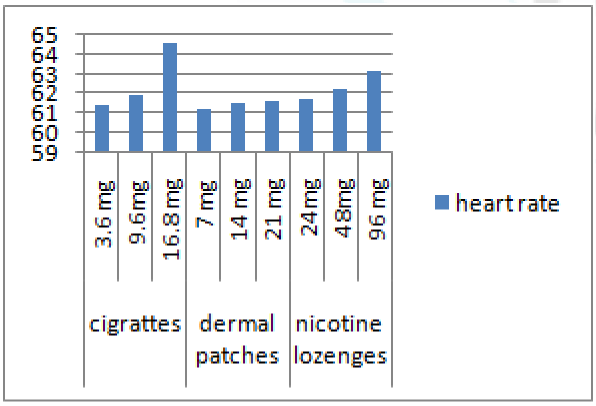

Figure 7: Heart Rate analyses

Modeling

PBTK modeling:

The Physiology Based Toxico-Kinetic modeling is simulated for both liver and kidney using MATLAB/Simulink. The simulation is given in figure 8 for kidney and figure 9 for liver and their respective output is presented in the figure 8a) and 9a). The analysis is also determined for blood concentration based on this that is explained in the analysis part of figure 6.

As a result from this modeling it is analyzed that the concentration of blood increases. In our human body, generally the concentration of blood should be minimum so that the blood can flow easily. Otherwise it will be very difficult for the blood to move freely. Because of this the organs are not supplied with rich oxygenated blood. Hence there may dis-function occurs. Thus the increased amount of nicotine intake affect the liver and kidney. They can't be able to do their proper function.

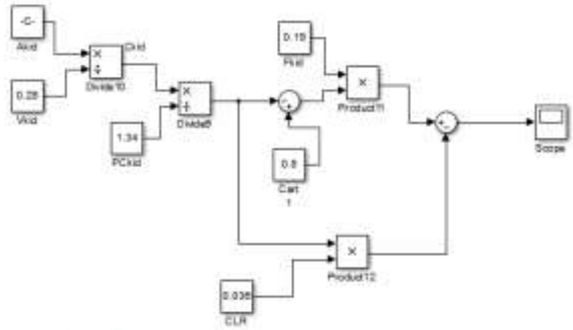

Figure 8: Modeling of kidney

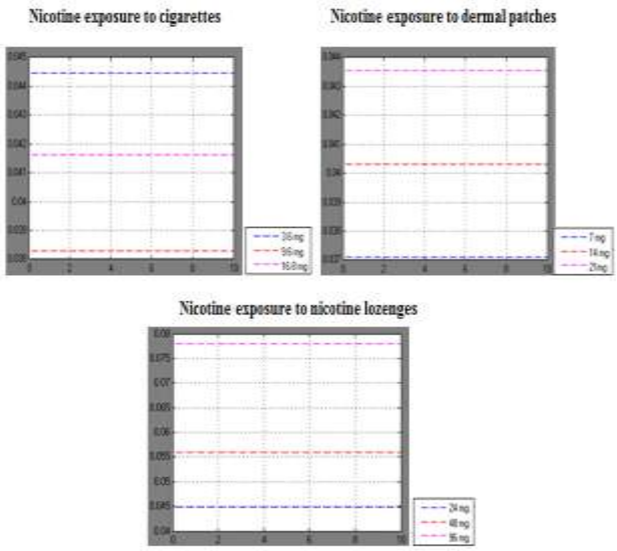

Figure 8 (a): simulation result for kidney at various nicotine dosages

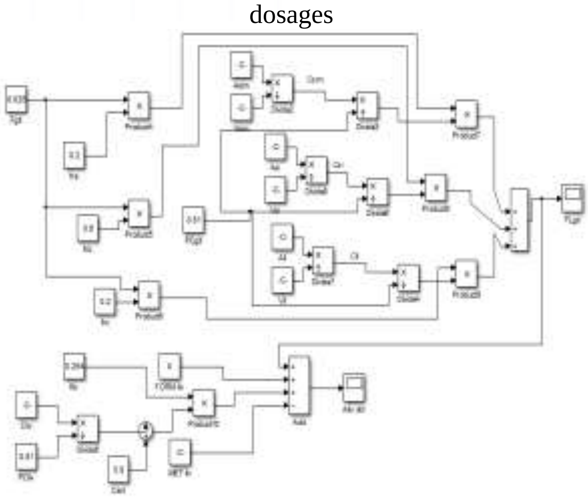

Figure 9: Modelling of Liver

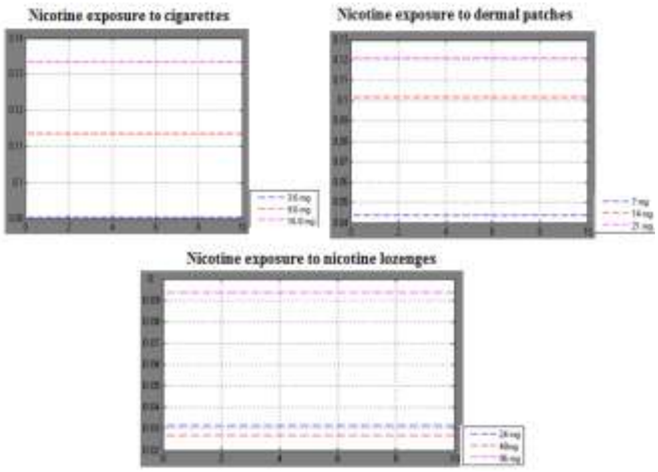

Figure 9 (a): simulation for liver at various dosages

PBTD modeling:

The Physiology Based Toxico-Dynamic modeling is simulated in MATLAB/Simulink. Here the simulation is done for occurring the heart rate which is represented in Figure 10 and their respective simulation output is given in figure 10 a)

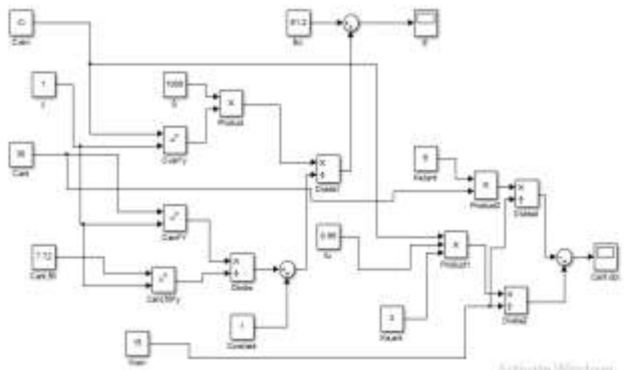

Figure 10: PBTD model

Table 6: PBTD & PBTK

	PBTK (Blood Concentrationin Organs)		PBTD (parameters of heart)	
	Liver	Kidney	Heart Rate	Cardiac Output
Cigrattes(1.2mg)				
3.6mg	0.0355	0.09026	71.27	4.704
9.6mg	0.0383	0.1135	71.4	4.712
16.8mg	0.0416	0.1334	74.64	4.926
Dermal patches				
7mg	0.0371	0.04376	71.2	4.699
14mg	0.0403	0.1019	71.49	4.718
21mg	0.0435	0.1213	72.06	4.756
Nicotine lozenges				
24mg	0.045	0.03168	71.69	4.732
48mg	0.056	0.02716	72.18	4.764
96 mg	0.078	0.09358	73.16	4.829

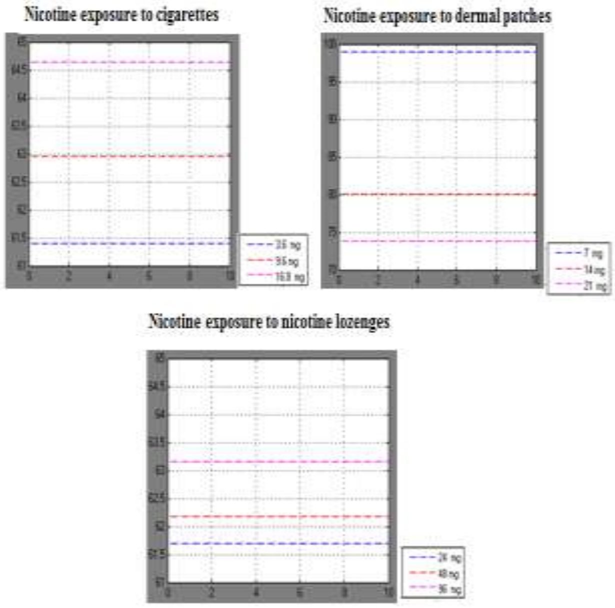

Figure 10: a) simulation result for PBTD modeling

As a result from this modeling it is analyzed that the rate of heart rate increases gradually based on the nicotine intake.

The table no:6 comprises of all information about the effect of blood concentration in liver, kidney and also the changes of heart rate and cardiac output based on nicotine intake which is analyzed in PBTD and PBTK modeling.

Combined heart and lung model

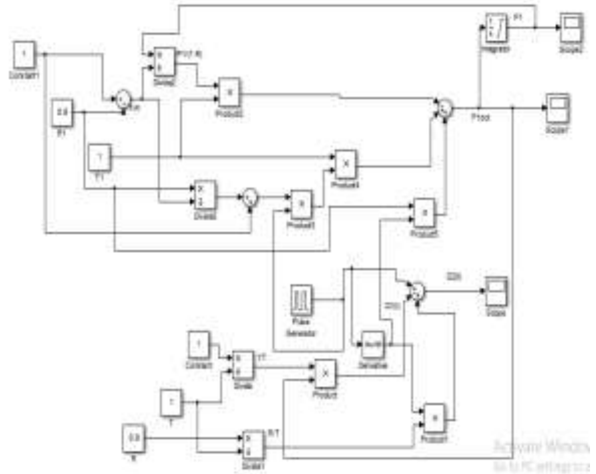

Figure 11: Model for combined heart and lungs.

By relating the heart and lungs , their modeling is done with the help of MATLAB/ Simulink. Here the pressure P1(pulmonary artery pressure) is determined which is given as input to the compliance chamber.

Thus the above modeling of heart- lung is simulated based on the equation 17 which is discussed in the paper by Jonathan et al.,. Before heart-lung model, the pulmonary artery pressure from right ventricle is determined which is given as input to the lung. Figure 7 shows the right ventricular pressure with respect to time (P1).

The compliance chamber designing is done in order to increase its efficiency based on the electrical network which is mentioned in the figure 5. This compliance chamber is combined along with the heart-lung model .

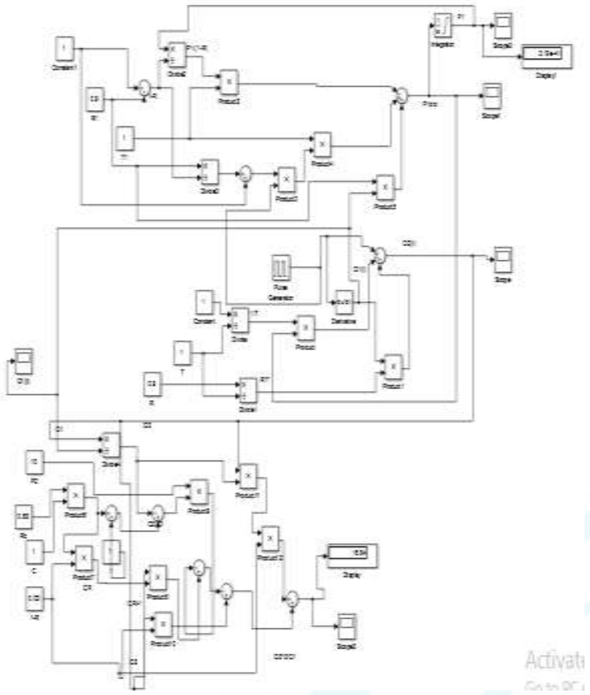

Figure 12: Compliance chamber model along with heart lung

Conclusion

As a result the acute effect of nicotine in human organs using Physiology Based Toxico-Kinetics (PBTK) and Physiology Based Toxico-Dynamics (PBTD) modeling for various nicotine dosages and their effects on acute increase in blood concentration and heart rate is analyzed , however the effects of smoking on heart rate are definitely higher than any of the investigated methods for nicotine theraphy. The apparent clearance of nicotine was slower in smokers than in non-smokers. The cardiac output for the analyzed heart rate is determined as well as the pressure and blood flow from the heart is given as input to the compliance chamber. The efficiency of the assisting device is increased by means of designing compliance-chamber.

References

[1] Bannon, Y. B., et al. "*Transdermal delivery of nicotine in normal human volunteers: a single dose and multiple dose study.*" European journal of clinical pharmacology 37.3 (1989): 285-290.

[2] Benowitz, Neal L., Florence Kuyt, and P. Jacob 3rd. "*Circadian blood nicotine concentrations during cigarette smoking.*" Clinical pharmacology and therapeutics 32.6 (1982): 758-764

[3] Brown, Ronald P., et al. "*Physiological parameter values for physiologically based pharmacokinetic models.*" Toxicology and industrial health 13.4 (1997): 407-484.

[4] Celsie, Alena, et al. "*A fugacity-based toxicokinetic model for narcotic organic chemicals in fish.*" Environmental Toxicology and Chemistry (2015).

[5] Elbourne, Diana, David Field, and M. Mugford. "*Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants.*" The Cochrane Library (2002).

[6] Fagerström, Karl. "*The nicotine market: an attempt to estimate the nicotine intake from various sources and the total nicotine consumption in somecountries.*" Nicotine & Tobacco Research 7.3 (2005): 343-350.

[7] Fattinger, Karin, DavideVerotta, and Neal L. Benowitz. "*Pharmacodynamics of acute tolerance to multiple nicotinic effects in humans.*" Journal of Pharmacology and Experimental Therapeutics 281.3 (1997): 1238-1246.

[8] Gajewska, M., et al. "*The acute effects of daily nicotine intake on heart rate–A toxicokinetic and toxicodynamicmodelling study.*" Regulatory Toxicology and Pharmacology 70.1 (2014): 312-324.

[9] Galletti, Pierre M., et al. "*A standardized method for defining the overall gas transfer performance of artificial lungs.*" ASAIO Journal 18.1 (1972): 359-368.

[10] Ghista, Dhanjoo N., et al. "*Lung Ventilation Modeling for Assessment of Lung Status: Detection of Lung Disease and Indication for Extubation of Mechanically-Ventilated COPD Patients*". INTECH Open Access Publisher, 2012.

[11] Haft, Jonathan W., et al. "*Effect of artificial lung compliance on rightventricular load.*" ASAIO journal 51.6 (2005): 769-772.

[12] Haft, Jonathan W., et al. "*Design of an artificial lung compliance chamber for pulmonary replacement.*" ASAIO journal 49.1 (2003): 35-40.

[13] Hlavac, Martin, and J. Holcik. "*Windkessel model analysis in MATLAB.*" Proc 2004 Student Electrical Engineering, Information and Communication Technologies, Brno 2004 (2004): 1-5.

[14] Kay, J. D., and Barbara S. Fox. "*Tolerability and pharmacokinetics of single and repeated doses of nicotine with The Straw, a novel nicotine replacement product.*" Nicotine & tobacco research 6.1 (2004): 63-70.

[15] Krüse, Jacob, et al. "*Analysis, interpretation, and extrapolation of dermal permeation data using diffusion-based mathematical models.*" Journal of pharmaceutical sciences 96.3 (2007): 682-703.

[16] Loizou, George D., and Martin Spendiff. "*A human PBPK model for ethanol describing inhibition of gastric motility.*" Journal of molecular histology 35.7 (2004): 687-696.

[17] Mendelson, Jack H., et al. *"Effects of smoking successive low-and high-nicotine cigarettes on hypothalamic–pituitary–adrenal axis hormones and mood in men."* Neuro psycho pharmacology 33.4 (2008): 749-760.

[18] Najem, Boutaïna, et al. "*Acute cardiovascular and sympathetic effects of nicotine replacement therapy.*" Hypertension 47.6 (2006): 1162-1167.

[19] Phillips, Rob, et al. "*Noninvasive cardiac output measurement in heart failure subjects on circulatory support.*" Anesthesia & Analgesia 108.3 (2009): 881-886.

[20] Porchet, HEAVE C., NEAL L. Benowitz, and LEWIS B.Sheiner. "*Pharmaco-dynamic model of tolerance: application to nicotine.*" Journal of Pharmacology and Experimental Therapeutics 244.1 (1988): 231-236.

[21] Schmitt, Walter. "*General approach for the calculation of tissue to plasma partition coefficients.*" Toxicology in Vitro 22.2 (2008): 457-467.
[22] Teeguarden, Justin G., et al. "*A multi-route model of nicotine–cotinine pharmacokinetics, pharmacodynamics and brain nicotinic acetylcholine receptor binding in humans.*" Regulatory Toxicology and Pharmacology 65.1 (2013): 12-28.
[23] Yamaguchi, Koji, et al. "*Structure–permeability relationship analysis of the permeation barrier properties of the stratum corneum and viable epidermis/dermis of rat skin.*" Journal of pharmaceutical sciences 97.10 (2008): 4391-4403.
[24] Yun, Hwi-yeol, et al. "*Effects of smoking on the pharmacokinetics and pharmacodynamics of a nicotine patch.*" Biopharmaceutics& drug disposition 29.9 (2008): 521-528.

Author Profile

S.Chandiyauma received Bachelor's degree in Electrical and Electronics Engineering from National Engineering College, Kovilpatti and received Master degree in control and instrumentation engineering from Thiagarajar College of Engineering, Madurai.

Dr.R.Helen received Bachelor's degree in instrumentation and control engineering from Bharath Institute of science and technology ,Madras university and M.E , Ph.D degree in Medical electronics and medical image segmentation from Anna University, Chennai.

She works as LECTURER for 3 years in Thangavelu Engineering college, Chennai. Worked as LECTURER for 3 years in srisairam engineering college, Chennai and now working as ASSISTANT PROFESSOR for 6 years in Thiagarajar College of Engineering , Madurai.