PBPK MODELING OF CAFFEINE AND COMPARISON OF PHARMACOKINETIC PARAMETERS AFTER DMINISTRATION AS AN INTRAVENOUS INFUSION, INTRAVENOUS BOLUS, AND ORAL SOLUTION

Abstract

PBPK modeling is a tool for the simulation of the pharmacokinetic parameters of drugs with respect to the different physiological parameters of the human and different physicochemical parameters of drug molecules such as body and organ weights, blood flow, partition coefficient, lipophilicity, solubility, etc. Caffeine is a **natural** alkaloid that is generally found in coffee beans, tea leaves, **and** cocoa beans. It is a central nervous system stimulant used in pain remedies. It has adverse effects also. The normal individual and population were created. The parameter used in the normal population were age – 32- 39years (mean- 35year), height- 152-170cm (mean- 165cm), weight- 66- 88kgs (mean- 70kg). The compound caffeine was created by different Physicochemical and ADME parameters of the drugs. Then the formulation tab was created for parenteral and oral administration. Then the administration protocol was created. Then the simulation was run for populations. After performing all the simulations all the pharmacokinetic parameters were collected and compared. The parameter values of IV bolus administration were AUC= 1750.49 µmol*min/l, C_{max}= 30.58 µmol/l, MRT= 2.69h, T_{max}= 0.05h, half-life= 2.81h. The parameter values of IV infusion administration were AUC= 1784.53 µmol*min/l, C_{max}= 11.24 µmol/l, MRT= 2.64h, T_{max}= 1h, half-life= 2.78h. The parameter values of oral administration were AUC= 1377.36 µmol*min/l, C_{max}= 5.71 µmol/l, MRT= 5.05h T_{max}= 0.07h, half-life= 5.71h. The simulation of pharmacokinetic profiles of caffeine after administration as 100 mg IV bolus, 100 mg IV infusion, major differences were found among the AUC, T_{max}, C_{max}, and $T_{1/2}$, and MRT. The oral solution had ~79% bioavailability. Oral administration had significantly reduced the C_{max}, but increased the MRT and half-life.

Keywords: Caffeine, Stimulant drug, Insilico study, Open System Pharmacology, PBPK model

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I. INTRODUCTION

One of the methylxanthine categories of central nervous stimulants is caffeine. Caffeine is a purine-based natural alkaloid. Generally, the major source of caffeine is coffee. Caffeine is also found in tea leaves, cocoa beans, etc. plants. Caffeine is mainly used in pain remedies. Other than pain remedies caffeine is also used as a diuretic, bronchial and cardiac stimulant. It is also used in different skin disorders. It has adverse effects also, the toxic dose of caffeine is more than 10grams per day.[1] Caffeine generally blocks the adenosine A1 and A2a receptors and produces its effects. Caffeine is generally an odorless powder, it is also bitter in taste. At room temperature, it is moderately soluble in water and organic solvents but at higher temperatures, caffeine is better soluble in water.[2]. The circulating blood system connects compartments in PBPK models, which correspond to different tissues in the body. PBPK modeling and simulation are currently receiving a lot of interest in drug research and development as well as regulatory filings and reviews.[3] PBPK modeling has an important role in drug discovery and development along with preclinical and pharmacological studies. At first, the animal PBPK models are simulated by using the available animal in vitro data and the compound's physicochemical data. To validate the assumptions of the model comparison of the simulations and actual in vivo data is done. After passing the animal simulation human PBPK models are simulated by using available human in vitro data, and the compound's physicochemical data. PBPK modeling is generally used as the first in-vitro in human clinical trials to predict the pharmacokinetic parameters of the drug molecule. Different body tissues and organs such as bone, brain, gut, kidney, heart, lungs, liver, skin, muscle, spleen, etc. are the main components of the PBPK models and all the tissues and organs are connected through the circulating blood system.[4]

II. METHOD

1. At 1st European adult males individuals are created of 35years age along with 70kgs weight and 165cm height. CYP1A2 is selected as the main metabolizing enzyme.
2. Then population is created with 100 numbers of the previous individual. The population has individuals of the range of 32- 39 years of age along with 66- 80kgs weight and 152- 170cm height.
3. The physicochemical properties of caffeine molecule such as lipophilicity, fraction unbound, molecular weight, presence of halogens, Effective molecular weight, Pka value, and solubility are inserted and the ADME parameters of caffeine such as specific intestinal permeability, hepatic clearance plasma clearance, biliary clearance related data are inserted. All the data are collected from the websites reputed websites such as drug bank, PubChem, etc
4. Formulations is created for the intravenous bolus, intravenous infusion, and oral solution.
5. Administration protocol is created for 100mg iv bolus, 100mg infusion for 60mins, and 100mg/5ml oral solution.
6. Finally run the simulation for adult populations using the different protocols and different pharmacokinetic parameters are observed and compared.

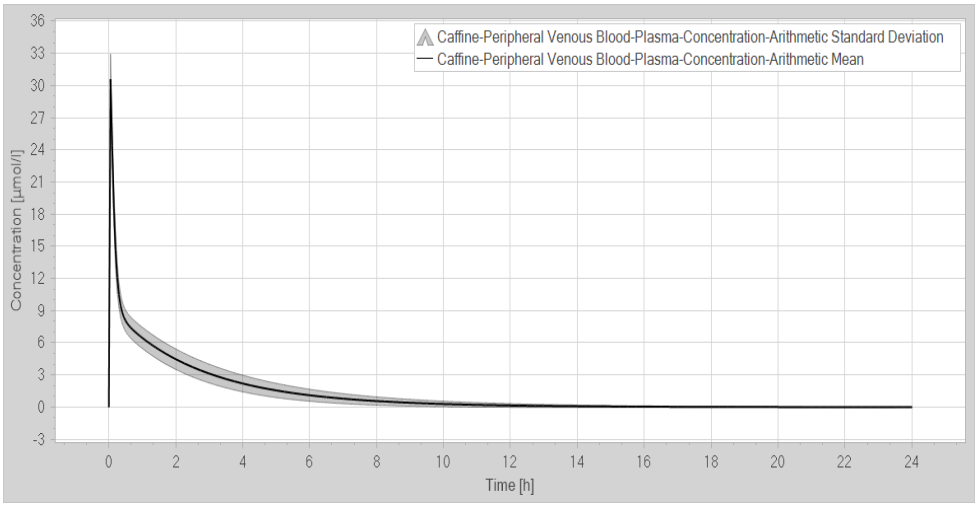

Figure 1: Simulation of caffeine after administration of 100mg IV bolus dose

III. RESULT & DISCUSSION

Table 1: Pharmacokinetic Data of Caffeine after Administration of 100mg IV Bolus Dose

	Caffeine – Caffeine **-Peripheral Venous Blood -Plasma -Concentration - Arithmetic Mean**
AUC [µmol*min/l]	1750.49
C_{max} [µmol/l]	30.58
MRT [h]	2.69
T_{max} [h]	0.05
Half-Life [h]	2.81

After performing the simulation of caffeine after the administration of 100mg IV bolus dose we observed the AUC= 1750.49 µmol*min/l, C_{max}= 30.58 µmol/l, MRT= 2.69h, T_{max}= 0.05h, half-life= 2.81h which is shown in the table no 1.

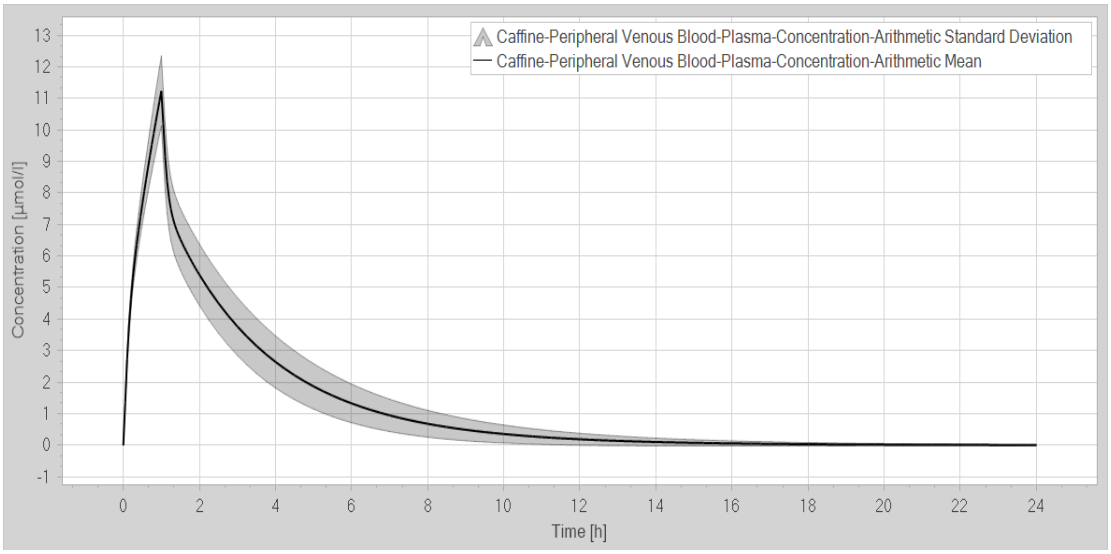

Figure 2: Simulation of caffeine after administration of 100mg IV infusion dose

Table 2: Pharmacokinetics Data of Caffeine after Administration of 100mg IV Infusion Dose

	Caffeine – Caffeine **- Peripheral Venous Blood – Plasma - Concentration - Arithmetic Mean**
AUC [µmol*min/l]	1784.53
C_{max} [µmol/l]	11.24
MRT [h]	2.64
T_{max} [h]	1
Half-Life [h]	2.78

After performing the simulation of caffeine after the administration of 100mg IV infusion dose we observed the AUC= 1784.53 µmol*min/l, C_{max}= 11.24 µmol/l, MRT= 2.64h, T_{max}= 1h, half-life= 2.78h which is shown in the table no 2.

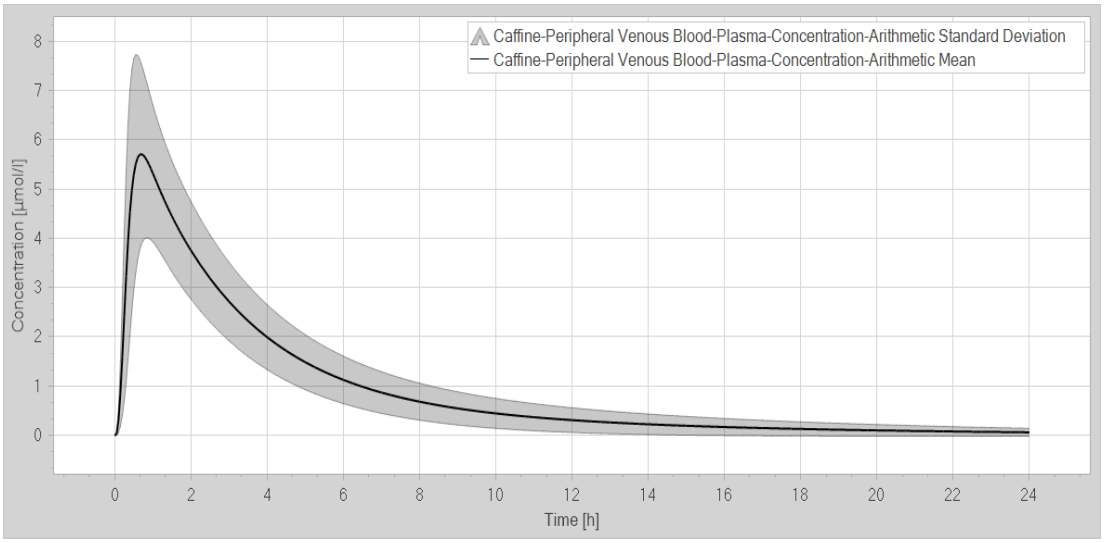

Figure 3: Simulation of caffeine after administration of 100mg/5ml oral solution dose

Table 3: Pharmacokinetics Data of Caffeine after Administration of 100mg/5ml Oral Solution Dose

	Caffeine – Caffeine - **Peripheral Venous Blood – Plasma - Concentration - Arithmetic Mean**
AUC [µmol*min/l]	1377.36
C_{max} [µmol/l]	5.71
MRT [h]	5.05
T_{max} [h]	0.7
Half-Life [h]	5.71

After performing the simulation of caffeine after the administration of 100mg/5ml oral solution dose we observed the AUC= 1377.36 µmol*min/l, C_{max}= 5.71 µmol/l, MRT= 5.05h, T_{max}= 0.7h, half-life= 5.71h which is shown in the table no 3.

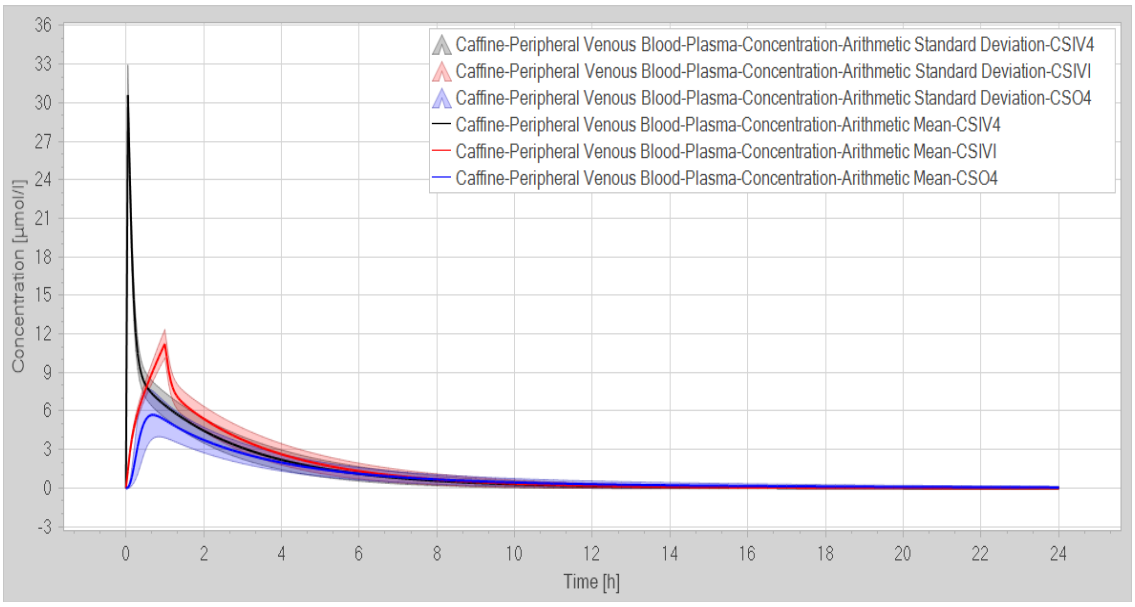

Figure 4: Simulation comparison of caffeine after administration of all dose

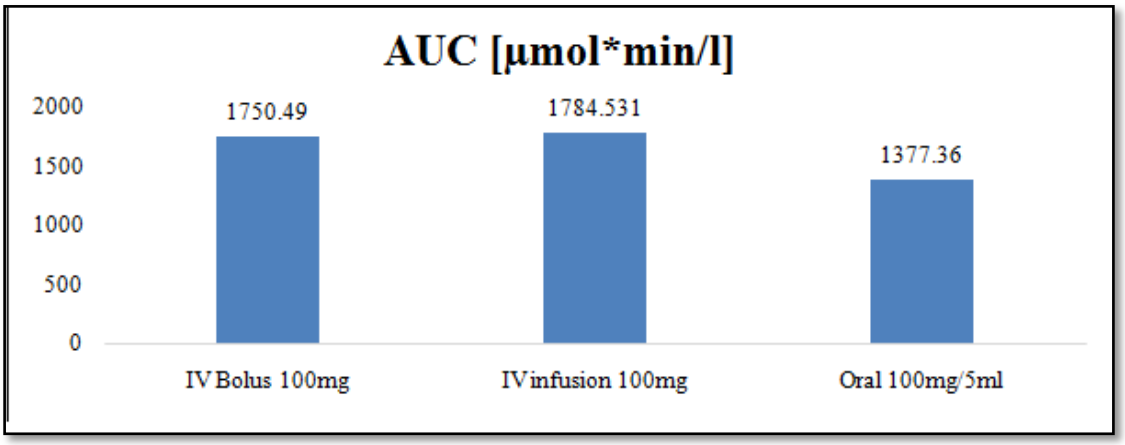

Figure 5: Comparison of AUC between IV bolus, IV infusion, and oral solution dose

Comparisons between the AUC of IV bolus, IV infusion, and oral solution are shown in figure no 5. No such difference is observed in all AUCs.

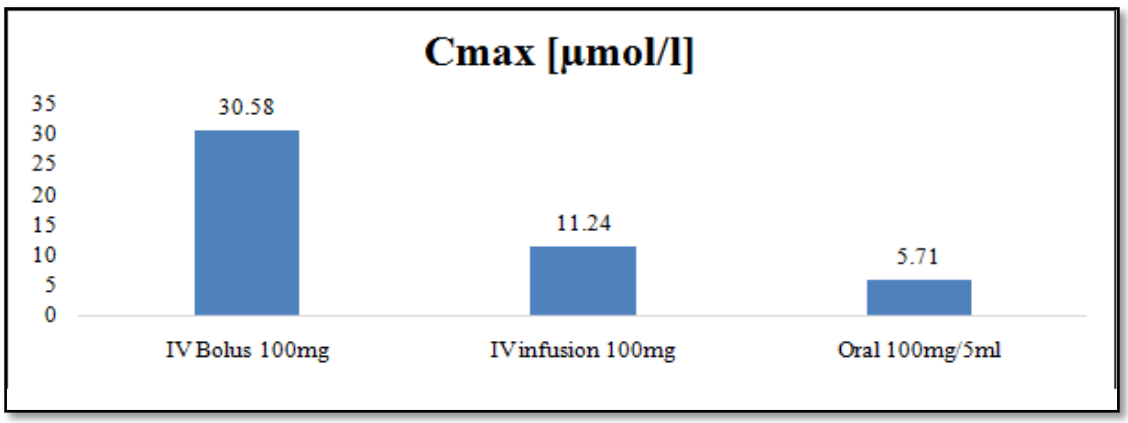

Figure 6: Comparison of C_{max} of caffeine after administration as IV bolus, IV infusion, and oral solution.

Comparisons between the C_{max} of IV bolus, IV infusion, and oral solution are shown in figure no 6. Highest C_{max} is observed in bolus dose and it is gradually decreased in infusion dose and oral dose.

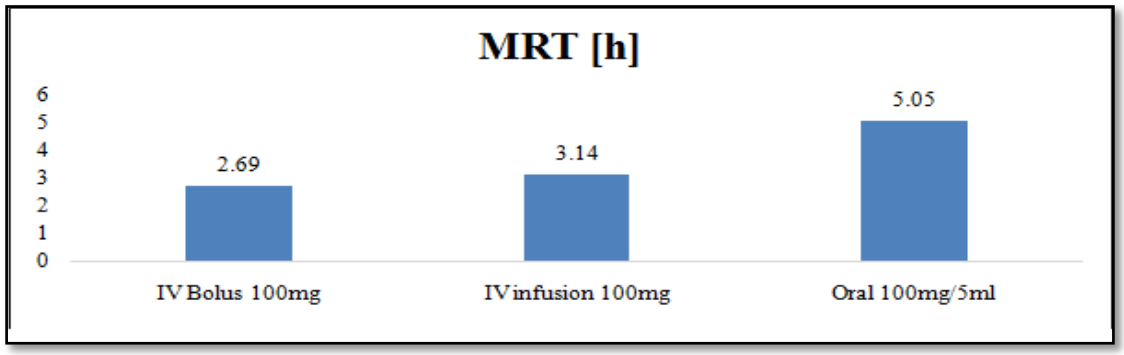

Figure 7: Comparison of MRT after administration of caffeine as IV bolus, IV infusion, and oral solution.

Comparisons between the MRT of IV bolus, IV infusion, and oral solution are shown in figure no 7. A slight difference is observed in all MRT. The lowest MRT is observed in IV bolus administration and the highest MRT is observed in oral solution administration.

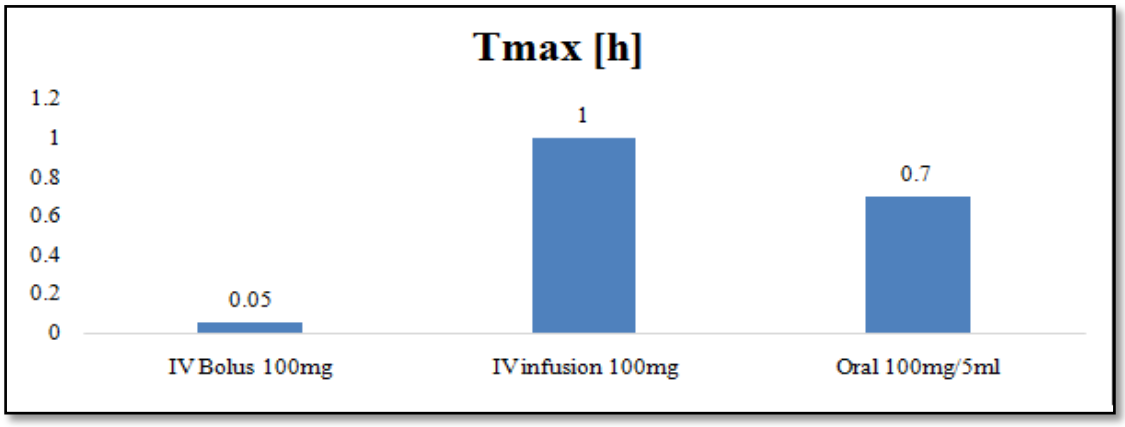

Figure 8: Comparison of T_{max} after administration of caffeine as IV bolus, IV infusion, and oral solution

Comparisons between the T_{max} of IV bolus, IV infusion, and oral solution are shown in figure no 8. In the case of IV bolus dose, the T_{max} was the minimum, indicating a sharp rise of C_{max} within a short period of time. In the case of IV infusion, with 1hour of infusion time, the highest plasma concentration is reached after 1hour. So the highest T_{max} is observed which is 1hour. In the case of oral solution, the highest plasma concentration was reached after ~42 minutes (T_{max} was 0.7 hours).

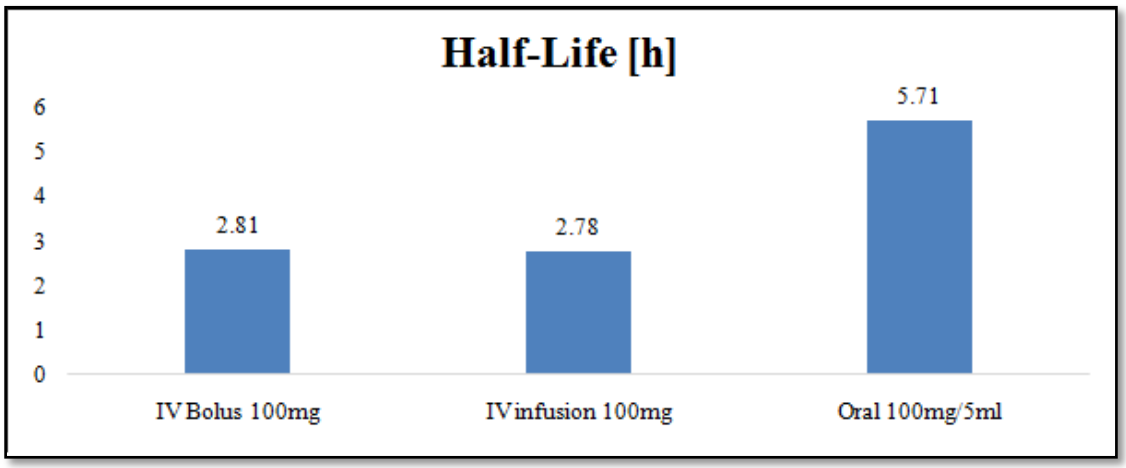

Figure 9: Comparison of Half-life between IV bolus, IV infusion, and oral solution dose

Comparisons between the half-life of IV bolus, IV infusion, and oral solution are shown in figure no 9. In the case of IV bolus and IV infusion dose, the half-life is almost similar. But in the case of oral solution dose the half-life increased and reached almost double than that of IV bolus or IV infusion dose.

IV. CONCLUSION

The simulation of pharmacokinetic profiles of caffeine after administration as 100 mg IV bolus, 100 mg IV infusion, major differences were found among the AUC, T_{max}, C_{max}, and $T_{1/2}$, and MRT. The oral solution had ~79% bioavailability. Oral administration had significantly reduced the C_{max}, but increased the MRT and half-life.

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