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Computer Simulation in Pharmacokinetic and Pharmacodynamic Studies

Durgawati Patel[1] and Puspendra Kumar[2]*

[1]*Department of Chemistry, Banasthali University, India*

[2]*KIET School of Pharmacy, KIET Group of Institutions, India*

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***Corresponding author:** Puspendra Kumar, KIET Group of Institutions, India, Email: puspendrapatel9@gmail.com

Abstract

Computer simulation in the field of Pharmacokinetic and Pharmacodynamics or in silica model is need of the hour in the biomedical field. In silica studies helps the research with ease and effectiveness. The current review summarises the various computer simulation models for different drugs with their outcomes. The current field is still under developed and needs more number of researches to achieve the goals.

Keywords: Computer simulation; Pharmacokinetic; Pharmacodynamics; Monte carlo simulation; In-silico studies

Mini Review

Current scenario is based on rapid development of technologies and computer simulation is an integral part in the field of pharmacokinetic and pharmacodynamics studies. It helps to rapid development of dosage forms with cheaper price and by using less manpower [1]. Medical field is still slow in accepting the computer simulation models. Simulation can play a major role for selection of studies to be performed; clinical trial simulation covers many disciplines i.e. pharmacokinetics, pre clinical pharmacologist, statistician, computer programmer etc. So, all experts can discuss and precede the appropriate research [2]. Understanding of the aim and objectives of the work is very essential for all experts and it's a tedious job; and the main reason behind the less development of the simulation technique in the field of medical field [3].

Computer simulation methods are based on availability of literature and studies regarding pharmacokinetic and pharmacodynamics parameters of the selected drugs [4]. Success of computer simulations methods are depended on quality of data inputs available [5]. Previous studies are taken as a reference to predict the simulation; and computer simulations demonstrate the pharmacokinetic parameters (i.e. half lives) of different drugs [6]. Computer simulations can give atomic details which are not accessible from experiments and help to elucidate the mechanism of the passive permeation process at a molecular level [7].

Current Development in Computer Simulation

All the medicines should undergo to a development and assessment processes before launching to the market. Safety of the patient is main concern for everyone especially in the case of drugs; so scrutiny and rigorous testing of the product before commercialization is highly essential. Some products fall into the potential harmful substances and repeated preclinical and clinical studies are harmful for animals and humans; so computer simulation can fill the gap and gives better result. Currently computer simulation models are promoted to overcome all these issues, but still this area is under developed and requires more development (Table 1) [8-10].

Table 1: Details do drugs investigated by various computer simulation models for pharmacokinetic and pharmacodynamic studies.

S. No.	Drug Under Investigation	Drug Under Investigation	Simulator Details	Outcome	References
1.	Fentanyl, alfentanil and sufentanil	Simulation of the plasma and effect site opioid concentrations after bolus injection.	80386 computer running MS-DOS (Microsoft, Redmond, WA) using program written in the C language by Steven L. Shafer	The simulation predicts fentanyl, alfentanil and concentrations of 1.8, 88 and 0.99ng/ml respectively.	[6]

2.	Paracetamo	Pharmacokinetic and dynamic model was applied to predict the dosing schedule of paracetamol to maintain the steady state plasma concentration. The study is based on the study of children aged 1 to 17 years.	Computer modelling using pharmacokinetic dynamic simulation with MKMODEL program.	70mg/kg loading dose and 50mg/kg maintenance dose was predicted by simulation to achieve the satisfactory therapeutic effect.	[4]
3.	Corticosteroids	Corticosteroid pharmacokinetics in the cochlear fluids for inner ear disorders.	Simulated with a finite element computer model, the Washington University Cochlear Fluids Simulator, version 1.6	The application protocol has a significant effect on the drug levels achieved in per lymph, with different delivery strategies resulting in very different amounts of drugs in the per lymph	[11]
4.	Small molecules (Water, acetamide, acetic acid, ethane, methylamine, methanol, methyl acetate, benzene)	Understanding passive membrane permeation for rational drug design	Atomistic molecular dynamics (MD) simulations to calculate lipid membrane permeability coefficients. All of the simulations were run in parallel with 4 processors, using version 27 of the CHARMM software package.	Permeability coefficients for eight small organic molecules have been calculated by means of MD simulations. Solubility-diffusion model as applied in the context of molecular dynamics computer simulations is able to reproduce the relative permeability's of eight small molecule	[7]
5.	Meropenem	Meropenem is a carbapenem antibiotic with a very broad spectrum of activity that makes it a good choice for the empirical therapy situation. Pharmacokinetic calculations were done by use of a two-compartment open model. The study was done for two doses.	Monte Carlo simulations for 10,000 simulated subjects for pharmacodynamic evaluation	high-dose continuous infusion has a robust probability of target attainment up to an MIC of 4 mg/ litre. The lower-dose probability of target attainment is still robust up to an MIC of 2 mg/litre.	[12]
6.	Farnesyl pyrophosphate synthase (FPPS)	FPPS is key cellular intermediate in isoprenoid metabolic pathways. On the basis of structural and kinetic data, different catalytic mechanisms have been proposed for FPPS.	Computation simulations were performed at the density functional theory (DFT) level with the SIESTA.	Results are relevant for the understanding of this important class of enzymes and for the design of more potent and specific inhibitors for the treatment of parasitic diseases.	[13]
7.	CNS drug (R1315)	Oral bioavailability prediction was studied as a function of the particle size and drug solubility.	Computer simulations were performed with the software Gastro Plus TM V.4.0 (Simulations Plus Inc., Lancaster, USA),	Simulation together with the statistically designed dog study provided a thorough biopharmaceutical assessment of the new CNS drug.	[5]

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8.	Lipophilic drugs (Danazol, Dipyridamole, Efavirenz, Exemestane, Gefitinib, Griseofulvin, Ivermectin, Ketoconazole, Ketoprofen, Nitrendipine, Phenytoin, Spironolactone)	For the models of poorly water-soluble drugs, neutral, free weak acid, and free weak base drugs were selected.	Runge-Kutta method used in STELLA 5.1.1 software (Cognitus Ltd., North Yorkshire, UK).	The mini scale dissolution test integrated with a computer simulation system could simulate quantitatively the in vivo absorption of structurally diverse BCS class II drugs.	[14]
9.	Methylprednisolone	Computer simulations allow application protocols and drug delivery systems to be evaluated, and may permit animal studies to be extrapolated to the larger cochlea of the human.	3D model was implemented in a commercial software package for finite-element calculations (ANSYS ®, ANSYS Inc., Canonsburg Pa., USA)	3D computations demonstrate the existence of substantial gradients across the scale in the basal turn.	[15]
10.	Insulin	subcutaneous (SC) insulin absorption model for computer simulation in a clinical diabetes	AIDA insulin PK model	Ability of the model to capture the fundamental dynamics of insulin action for several insulin types based on data from a wide range of studies using a unified consistent PK model.	[16]
11.	Erlotinib	Selected model predicted that CYP3A4 contributed to ~70% of the metabolic elimination of erlotinib, with CYP1A2 being responsible for the other ~30%. A drug-drug interaction study was therefore conducted for erlotinib	Simulation model, SimCYP™	Prediction of clinically important drug-drug interaction with SimCYP™using in vitro human metabolism data can be a powerful tool during early clinical development	[17]
12.	Doxorubicin and cisplatin	Investigation of the pharmacokinetics and effect of selected drugs in vascularised tumours by two-dimensional simulations.	Computer (in silico) simulations based on mathematical modelling and calibrated with experimental data	Computational models have the potential to facilitate an era of great discovery and progress in understanding and treating cancer	[18]
13.	BCS class I drugs (propranolol and metoprolol) and BCS class III drugs (cimetidine, atenolol, and amoxicillin)	In silico bioequivalence studies to assess the feasibility of extending bio waivers to BCS class III drugs	Simulation was done by Gastro Plus (version 6.0)	The results of Gastro Plus simulations indicate that the dissolution rate of BCS class III drugs could be prolonged, rather than permeability.	[19]
14.	carbamazepine (CBZ) and its main active metabolite carbamazepine-10,11-epoxide (CBZE)	CBZ and CBZE time-concentration profiles in various scenarios were generated based on a population pharmacokinetic study using Monte Carlo simulation	Monte Carlo simulations with $SIMULATION block in the NONMEM software (Version 7.2; Icon Inc, PA, USA) with the ONLYSIM-ULATION and SUBPROBLEMS option	The risk for a sub-therapeutic range of CBZ and CBZE was increased in a dose-dependent manner	[20]

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Conclusion

More number of research and experts are required in the field of in silico computer simulation field to improve the product trials and replacement of animals and human during clinical trials. Subject specific model studies are recommended in which living models can be easily replaced by in silico models. The major challenge in the field of in silico pharmacokinetic and Pharmacodynamic studies is the harmony of understanding between the pharmacokinetics and computer programmer.

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