International Journal of Current Research in Medicines & Medical Science
Vol. 3, Issue 1 – 2020
ISSN: 2582-1628

Prediction Analysis of Pharmacokinetic, Toxicological and Druglikeliness Parameters of Several oral Hypoglycemic Agents of Sulfonyl Ureas Second Generation using in-Silico Methods

Nitesh Raikwar[1], Ashwani Mishra[2]
[1]*Department of Pharmacy, Barkatullah University, Bhopal.*

Abstract

Sulfonylureas are widely used in treatment of Diabetes as a hypoglycemic agent due to its safe and effective use. In this research work an Effort is made to analyze the second generation Sulfonylureas on the basis of insilico toxicity study, ADME sar study and Drug likeliness properties. The four drugs which used in this insilico research work are glibenclamide, gliclazide, glipizide, and glimepiride.In this study it has been observed that all the drugs were within the bioavailabily radar. The best skin permeability score was exhibited by glimepiride and Highest gastrointestinal absorption. glibenclamide revealed violation of Lipinski rule of 5 as compared to other three drugs. In the case of in-silico toxicity study some sign of liver toxicity has been observed with Glebenclamide. On the basis of Physiochemical properties, druglikeliness study and skin permeability study Glimepiride proved its better therapeutic profile as compared to other three drugs in the study.

Introduction

The ninth edition of the International Diabetes Federation Diabetes Atlas, It is projected that just over 134 million Indians will be diabetics in coming 25 years. As per their Prediction One in six people with diabetes in the world is from India[1].

There are many types and classes of drug which has been used as oral hypoglycemic agent in the treatment of Diabetes and one of them is Sulfonylureas SUs,Which is still widely recommended, prescribed and use as safe and effective Hypoglycemic Agent[2]. Most international and regional guidelines prefer Sulfonylureas, with gliclazide. It has been mentioned that Sulfonylureas is good for CV and renal safety. Sulfonylureas are effective, well-tolerated and inexpensive treatments for T2DM, and widely recommended as add-on therapy in evidence-based international consensus reports[3,4]. Sulfonylureas are effective first-line treatment of choice in the majority of patients with MODY[5,6].

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Among the available sulfonylureas, gliclazide has been showed greatest beneficial impact on cardiovascular mortality, and the lowest incidence of severe hypoglycaemia. which make it safe[7].

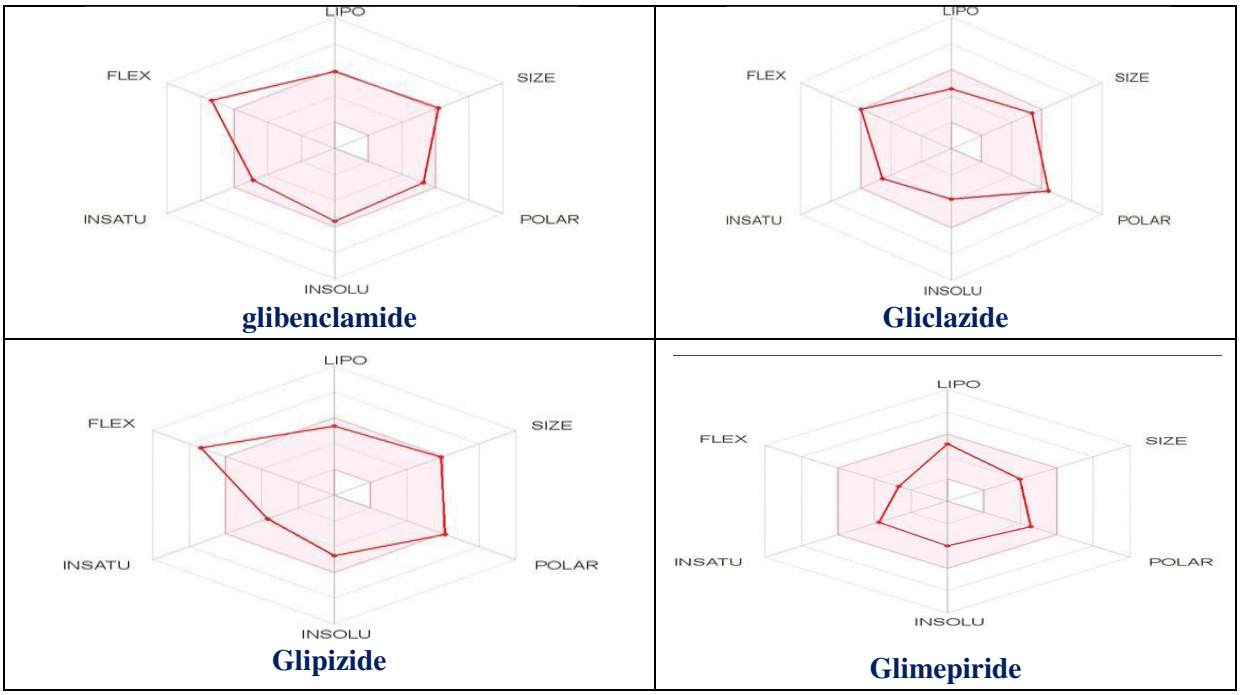
In silico tools and simulation studies have gained sufficient attention of the research community and they help to sort of many research problem. For absorption, distribution, metabolism, excretion, and pharmacokinetics (ADME-PK) properties investigation of new chemical entities are an important part of the present industrial drug discovery.

ADME properties have helped in systematic curation and analysis of ligand and target complex data[8]. Different review articles have been published which exhibit ADME, pharmacogenomics-related databases, potential drug-drug interaction information[9] pharmacovigilance databases and identified human drug safety data resources, specific to country.

This led to the aim of this study to perform in-silico study of Sulfonylureas second generation widely used oral hypoglycemic agents like glibenclamide, gliclazide, glipizide, and glimepiride and analyze their therapeutic potential using different insilico studies using online accessible software.

Material and Methods

These studies were conducted using online open accessible software The software used for the in-silico study was mainly coded in Python 2.7 The process of screening of Drug Molecules on the basis of Favorable properties generated by basis of in-silico physiochemical properties, ADME study and toxicological studies. following studies were conducted using online open accessible software The software used for the in-silico study was mainly coded in Python 2.7 The process of screening of molecule adopted on the basis of Favorable properties of oral hypoglycemic agent.



Result and Discussion

Pharmacokinetic study of glibenclamide, gliclazide, glipizide, and glimepiride revealed that maximum gastrointestinal absorption exhibited by the glimepiride as compared to other three drugs. All the drug were not permeable to Blood brain barrier, highest log Kp skin permeation was revealed by the glimepiride -5.79 cm/s.

The violation of drug likeliness property of Lipinski rule of 5 was showed by the Glibenclamide as compared to gliclazide, glipizide, and glimepiride though all the four drugs shows bioavilability score 0.55.

The bioavailability score radar plot enables a first glance at the drug-likeness of a molecule. The pink area represents the optimal range for each properties lipophilicity: XLOGP3 between −0.7 and +5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 $Å^2$, solubility: log S not higher than 6, saturation: fraction of carbons in the sp^3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds. In this example, the compound is predicted not orally bioavailable, because too flexible and too polar.

The physiochemical properties of glibenclamide, gliclazide, glipizide, and glimepiride exhibited highest molecular weight of Glibenclamide that is 515.9g/mol which might is outside the range of Lipinski rule of 5, although test of the physiochemical properties of all the drugs were within the acceptable range .

The insilico toxicity study revealed that glibenclamide has shown the sign of liver toxicity as per the simulation study done and rest all the three drugs gliclazide, glipizide, and glimepiride do not show any chance of liver toxicity and if we consider cytochrome inhibition effect of the drug then glibenclamide revealed inhibitory effect on 3A4, 2C9 and glipizide showed inhibition of 2C9. Membrane transporter based inhibition effect of P-gp inhibitor and P-gp Substrate inhibitor showed by Glibenclamide and Glipizide showed inhibitor effect of P-gp substrate of membrane transporter.

(Table 1, 2 and 3 end of the paper)

Conclusion

From this insilico study it could be concluded that Skin permeability and best gastrointestinal absorption was exhibited by Glimepiride which was good as compare to other three drug gliclazide, glipizide, and glimepiride. The insilico toxicity study of glibenclamide and glipizide exhibited membrane transport based inhibitory effect similarly metabolism based cytochrome inhibition effect of the glibenclamide and glipizide were observed. Glibenclamide even exhibited liver toxicity effect in the in silico toxicity study.

Acknowledgement

The authors are grateful to the Head Department of Pharmacy, Barkatullah University for her support and guidance.

Conflict of Interest

There is no conflict of interest.

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Table 1.Pharmacokinetic and Drug likeliness properties of all the oral hypoglycemic agents

Pharmacokinetics				
Hypoglycemic Agents	Glibenclamide	Gliclazide	Glipizide	Glimepiride
1. GI absorption	Low	Low	Low	High
2. BBB permeant	No	No	No	No
3. P-gp substrate	Yes	Yes	Yes	No
4. CYP1A2 inhibitor	No	No	No	No
5. CYP2C19 inhibitor	No	No	No	Yes
6. CYP2C9 inhibitor	No	Yes	Yes	Yes
9. Log K_p (skin permeation)	-6.03 cm/s	-7.29 cm/s	-6.56 cm/s	-5.79 cm/s
Druglikeness				
1. Lipinski	Yes; 1 violation: MW>500	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
2. Ghose	No; 1 violation: MW>480	Yes	No; 2 violations: MW>480, MR>130	Yes
3. Veber	No; 1 violation: Rotors>10	No; 1 violation: TPSA>140	No; 1 violation: Rotors>10	Yes
4. Egan	Yes	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>131.6	Yes
5. Muegge	Yes	Yes	Yes	Yes
6.Bioavailability Score	0.55	0.55	0.55	0.55
Medicinal Chemistry				
1. PAINS	0 alert	0 alert	0 alert	0 alert
2. Brenk	0 alert	2 alerts:	0 alert	2 alerts:
		imine_1, imine_2		imine_1, imine_2
3. Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5	No; 2 violations: MW>350, Rotors>7	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5	Yes
4. Synthetic accessibility	3.36	3.57	4.71	3.97

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Table 2.Physicochemical properties of all the oral hypoglycemic agents

PHYSIOCHEMICAL PROPERTIES					
1.	Oral Hypoglycemic agents	Glibenclamide	Gliclazide	Glipizide	Glimepiride
1.	Formula	C23H27ClN3NaO5S	C21H27N5O4S	C24H34N4O5S	C15H21N3O3S
2.	Molecular weight	515.99 g/mol	445.54 g/mol	490.62 g/mol	323.41 g/mol
3.	Num. heavy atoms	34	31	34	22
4.	Num. arom. heavy atoms	12	12	6	6
5.	Fraction Csp3	0.39	0.43	0.54	
6.	Num. rotatable bonds	11	9	11	4
7.	Num. H-bond acceptors	6	7	5	5
8.	Num. H-bond donors	2	3	3	2
9.	Molar Refractivity	126.81	117.17	133.31	88.79
10.	TPSA	109.95 Å²	142.02 Å²	133.06 Å²	
11	Solubility	Moderately soluble	soluble	Moderately soluble	soluble
12	Log S	-7.71	-6.18	-6.09	-3.07

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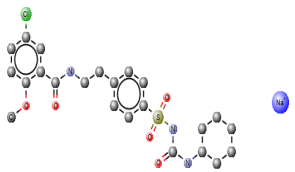
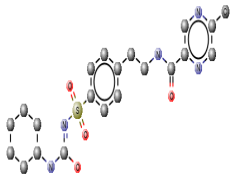
Table 3.in-silico toxicity study of all the oral hypoglycemic agents

Glibenclamide



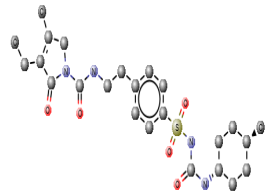
Liver Toxicity		Metabolism						Membrane Transporters			Others			
			Cyp Inhibitors for											
DILI	Cyto-toxicity	HLM	1A2	3A4	2D6	2C9	2C19	BBB	P-gp Inhibitor	P-gp Substrate	hERG Blocker	MMP	AMES	MRTD (mg/day)
Yes	⊘	⊘	No	Yes	No	Yes	No	No	Yes	Yes	No	No	No	183

Gliclazide



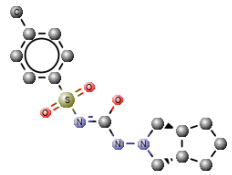
Liver Toxicity		Metabolism						Membrane Transporters			Others			
			Cyp Inhibitors for											
DILI	Cyto-toxicity	HLM	1A2	3A4	2D6	2C9	2C19	BBB	P-gp Inhibitor	P-gp Substrate	hERG Blocker	MMP	AMES	MRTD (mg/day)
⊘	⊘	⊘	No	No	No	⊘	No	⊘	⊘	⊘	No	No	⊘	15

Glipizide



Liver Toxicity		Metabolism						Membrane Transporters			Others			
			Cyp Inhibitors for											
DILI	Cyto-toxicity	HLM	1A2	3A4	2D6	2C9	2C19	BBB	P-gp Inhibitor	P-gp Substrate	hERG Blocker	MMP	AMES	MRTD (mg/day)
No	⊘	⊘	No	No	No	Yes	No	⊘	⊘	Yes	No	No	⊘	261

Glimepiride



Liver Toxicity		Metabolism						Membrane Transporters			Others			
			Cyp Inhibitors for											
DILI	Cyto-toxicity	HLM	1A2	3A4	2D6	2C9	2C19	BBB	P-gp Inhibitor	P-gp Substrate	hERG Blocker	MMP	AMES	MRTD (mg/day)
No	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘	No	⊘	⊘	⊘	⊘	⊘