The Pharmaceutical and Chemical Journal, 2017, 4(5):143-146

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Computational Prediction of Pharmacokinetic, Bioactivity and Toxicity Parameters of Some Selected Anti arrhythmic Agents

Shashank Shekhar Mishra[1]*, Neeraj Kumar[1], Gajaram Sirvi[1], Chandra Shekhar Sharma[2], Hamendra Pratap Singh[2], Harshda Pandiya[2]

[1*]Department of Pharmaceutical Chemistry, Geetanjali Institute of Pharmacy, Udaipur 313001, India
[2]Department of Pharmaceutical Chemistry, Bhupal Nobles' College of Pharmacy, Udaipur 313001, India

Abstract Many pharmacological agents are available for the treatment of cardiac arrhythmias. Arrhythmia may be classified on the basis of rate (bradycardia and tachycardia), mechanism (automaticity, re-entry, triggered) or duration (isolated premature beats; couplets). The treatment approach to arrhythmia depends firstly on whether or not the affected person is stable or unstable. This research investigation finds the various pharmacokinetic, bioactivity and toxicity parameters for some selected anti-arrhythmic agents for designing new agents.

Keywords Tachycardia, QSAR, ADMETox, Teratogenicity, MLogP

Introduction

Cardiac arrhythmias are caused by a disturbance in the conduction of the impulse through the myocardial tissue, by disorders of impulse formation, or by a combination of these factors. The Antiarrythmic agents used most commonly affect impulse conduction by altering conduction velocity and the duration of the refractory period of heart muscle tissue. Within the past 5 decades, research on normal cardiac tissues and, in the clinical setting, on patients with disturbances of rhythm and conduction has brought to light information on the genesis of cardiac arrhythmias and the mode of action of anti-arrhythmic agents [1].

Arrhythmia may be classified on the basis of rate (bradycardia and tachycardia), mechanism (automaticity, re-entry, triggered) or duration (isolated premature beats; couplets). The term cardiac arrhythmia covers a very large number of very different conditions.

The most common symptom of an arrhythmia is palpitation which is an awareness of an abnormal heartbeat. These may be infrequent, frequent, or continuous. Some of these arrhythmias are harmless (though distracting for patients) but some of them predispose to adverse outcomes [2].

Some arrhythmias do not cause symptoms, and are not associated with increased mortality. If an arrhythmia results in a heartbeat that is too fast, too slow or too weak to supply the body's needs, this manifests as a lower blood pressure and may cause dizziness or fainting [3].

The treatment approach to arrhythmia depends firstly on whether or not the affected person is stable or unstable. Treatments may include physical maneuvers, medications, electricity conversion, or electro- or cryo-cautery. In this research work, we performed computational investigation of different pharmacokinetic, bioactivity and toxicity parameters for design new agents to overcome the existing side-effects of current anti-arrhythmic drugs for better potency.

Materials and Methods

Pharmacokinetic Descriptor Calculation through Computational Approaches

There are various physicochemical descriptors and pharmacokinetic relevant properties of the anti-arrhythmic agents were evaluated by using the tool Molinspiration Cheminformatics server (http://www.molinspiration.com). Molinspiration Cheminformatics offers broad range of tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches. This software also supports fragment-based virtual screening, bioactivity prediction and data visualization. Molinspiration tools are written in Java, therefore can be used practically on any computer platform [4-5].

Drug-likeness is qualitative concept used for drug like property that described as a complex balance of various molecular properties and structural features which determine whether particular molecule is similar to the known drugs. These properties are mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features that influence the behaviour of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others. The Lipinski rule of five deals four simple physicochemical parameters ranges (MWT $\leq$ 500, log P $\leq$ 5, Hbond donor's $\leq$ 5, H-bond acceptors $\leq$ 10) associated with 90% of orally active drugs that have passed phase II clinical status [6]. There are several scoring methods such as ligand efficiency and lipophilic efficiency can be used to express drug likeness as measure of potency.

These physicochemical descriptors are associated with aqueous solubility and intestinal permeability within acceptable range.

In silico Toxicity Evaluation

The toxicity of the anti-arrhythmic agents was evaluated by computational method using Pallas version 3.1 ADMETox prediction software pentium IV processor. This software tool was started by double click on the icon. The molecule to be predicted was drawn by double click on new option, and then molecule was subjected for evaluation of toxicity by selecting ToxAlert options. Various types of toxicities including oncogenicity, neurotoxicity, teratogenicity, immunotoxicity, etc. were generated and toxicity profile of molecule noted.

Result and Discussion

There were some anti-arrhythmic agents were selected and analyzed to ADME properties and drug-likeness (Lipinski's rule of five) which are given in Table 1. All anti-arrhythmic agents have molecular weight in the range (MWT $\leq$ 500) except amiodarone. Low molecular weight containing molecules are easily absorbed, diffused and transported as compared to high molecular weight compounds. As molecular weight increases except certain limit, the bulkiness of the molecules are also increases comparably [7].

Table 1: Pharmacokinetic Properties of Antiarrythmic agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	*In silico* % absorption
Procainamide	$C_{13}H_{21}N_3O$	235.33	0.99	58.36	4	3	6	239.83	88.86
Mexiletine	$C_{11}H_{17}NO$	179.26	2.00	35.26	2	2	3	187.63	96.83
Propafenone	$C_{21}H_{27}NO_3$	341.45	3.46	58.56	4	2	11	338.04	88.79
Phenytoin	$C_{15}H_{12}N_2O_2$	252.27	2.18	58.20	4	2	2	223.89	88.92
Propranolol	$C_{16}H_{21}NO_2$	259.35	2.97	41.49	3	2	6	257.82	94.68
Flecainide	$C_{17}H_{20}F_6N_2O_3$	414.35	4.25	59.59	5	2	9	332.00	88.44
Lidocaine	$C_{14}H_{22}N_2O$	234.34	2.13	32.34	3	1	5	244.86	97.84
Amiodarone	$C_{25}H_{29}I_2NO_3$	645.32	8.31	42.68	4	0	11	437.04	94.27

All selected anti-arrhythmic agents have number of H-bond acceptors and number of Hbond donors is within range according to Lipinski's rule of five, so selected anti-arrhythmic agents have no violations except amiodarone which has one viiolation. The MLogP (octanol / water partition co efficient) of all agents were calculated and were found

to be within range according to Lipinski's rule except amiodarone. The MLogP value is used to calculate the lipophilic efficiency that measures the potency of drug. Therefore Octanol-water partition coefficient logP value is essential in rational drug design and QSAR studies. In the pharmacokinetic study, hydrophobicity of the molecule is assessed by evaluating logP value because hydrophobicity plays a vital role in the distribution of the drug in the body after absorption [8]. TPSA (Topological Polar Surface Area) is a very useful physiochemical parameter of molecule that gives the information about polarity of compounds. This parameter was evaluated for analyzing drug transport properties. Polar surface area is the sum of all polar atoms mainly oxygen and nitrogen including attached hydrogen [9]. Percent absorption were also evaluated for all selected anti-arrhythmic agents by %ABS = 109- (0.345 * TPSA) [10]. Molecular volume assesses the transport properties of the molecule such as blood-brain barrier penetration. The number of rotatable bond was calculated and have found relevant. A molecule which have more number of rotatable bond become more flexible and have good binding affinity with binding pocket.

Bioactivity of all selected anti-arrhythmic agents was evaluated against six different protein structures. Biological activity is predicted by bioactivity score that are categorized under three different ranges-

1. If bioactivity score is more than 0.00, having considerable biological activity.

2. If bioactivity score is 0.5 to 0.00, having moderately activity.

3. If bioactivity score is less than -0.50, having inactivity [11].

The result of this investigation was found that the selected anti-arrhythmic agents are biologically active and have physiological effect. The bioactivity score profile of the all selected agents is given in Table 2.

Table 2: Bioactivity of Antiarrythmic agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Procainamide	-0.09	0.01	-0.10	-0.70	-0.20	-0.04
Mexiletine	-0.40	0.10	-0.33	-0.55	-0.36	-0.26
Propafenone	0.27	0.09	-0.22	0.08	0.17	0.18
Phenytoin	0.07	-0.14	-0.47	-0.32	0.01	-0.02
Propranolol	0.12	0.06	-0.17	-0.19	-0.04	0.04
Flecainide	0.16	0.03	-0.04	0.01	0.20	-0.00
Lidocaine	-0.43	-0.39	-0.49	-0.68	-0.65	-0.34
Amiodarone	0.13	-0.07	-0.21	0.40	-0.08	0.06

The bioactivity score provide the information about the binding cascade of the drugs that is used for the development of a new functional drug with increased binding selectivity profile and less undesirable effects.

All selected anti-arrhythmic agents were evaluated to toxicity profile and given in Table 3. All of the drugs were found to be highly probable to toxicity except mexiletine. The interesting fact about toxicity is all selected anti-arrhythmic agents were found to be teratogenic and exhibits teratogenicity except mexiletine and phenytoin.

Table 3: Toxicity Profile of Antiarrythmic agents

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Procainamide	Highly Probable	76	76	51	19	0	29	0	0
Mexiletine	Not Probable	0	0	0	0	0	0	0	0
Propafenone	Highly Probable	76	76	0	53	0	0	29	0
Phenytoin	Highly Probable	76	76	0	0	0	0	0	0
Propranolol	Highly Probable	100	100	0	53	0	0	29	0
Flecainide	Highly Probable	76	76	71	17	0	0	0	0
Lidocaine	Highly Probable	81	76	81	17	0	0	0	0
Amiodarone	Highly Probable	100	100	91	38	0	0	0	0

These research findings provide the lead for the design and development of new anti-arrhythmic agents. Currently, all existing anti-arrhythmic agents having serious toxicity profile. Therefore, it is essential that the development of new anti-arrhythmic agents molecules with lesser side effects and toxicity.

Computational study of all selected anti-arrhythmic agents gives the information about the pharmacokinetics of the existing drugs that provide the lead for development of functional drug with more effectiveness and lesser toxicity.

References

1. Wilson, C. O., Beale, J. M., & Block, J. H. (2011). Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry. Lippincott Williams & Wilkins.
2. Demarie, D., Orlando, F., Imazio, M., Cerrato, E., Richiardi, E., & Belli, R. (2015). Real-World Observations with Dronedarone Compared to Other Anti-Arrhythmic Drugs in Recurrent Atrial Fibrillaton.
3. Glover, B. M., & Dorian, P. (2016). Anti-arrhythmic Drugs. In Clinical Handbook of Cardiac Electrophysiology (pp. 249-264). Springer International Publishing.
4. Sharma, C. S., Mishra, S. S., Singh, H. P., Kumar, N. (2016). In silico ADME and Toxicity
5. Study of Some Selected Antineoplastic Drugs. International Journal of Pharmaceutical Sciences and Drug Research, 8(1), 65-67.
6. Mishra, S. S., Sharma, C. S., Singh, H. P., Pandiya, H., & Kumar, N. (2017). In silico Pharmacokinetic and Toxicity study of Some Selected Antidepressant Drugs. Chemistry Research Journal, 2(1), 42-45.
7. Lipinski CA. Lead-and drug-like compounds: the rule-of-five revolution. Drug Discovery Today: Technologies. 2004; 1(4):337-341.
8. Srimai V, Ramesh M, Parameshwar KS, Parthasarathy T. Computer-aided design of selective Cytochrome P450 inhibitors and docking studies of alkyl resorcinol derivatives. Medicinal Chemistry Research. 2013; 22(11):5314-5323.
9. Abraham DJ. Burger's medicinal chemistry and drug discovery. Wiley Interscience, 2003.
10. Palm K, Stenberg P, Luthman, K, Artursson P. Polar molecular surface properties predict the intestinal absorption of drugs in humans. Pharmaceutical research. 1997; 14(5):568-571.
11. Sharma CS, Verma T, Singh HP, Kumar N. Synthesis, characterization and preliminary anticonvulsant evaluation of some flavanone incorporated semicarbazides. Medicinal Chemistry Research 2014; 23(11):4814-4824.
12. Verma A. Lead finding from *Phyllanthus debelis* with hepatoprotective potentials. Asian Pacific Journal of Tropical Biomedicine. 2012; 2(3): S1735-S1737.