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A REVIEW OF PHENYTOIN USED AS AN ANTIARRHYTHMIC AGENT

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ABSTARCT

Phenytoin, a hydantoin derivative, is primarily used as an anticonvulsant and has been recognized for its antiarrhythmic potential for a long time. Phenytoin has been classified as a Class IB antiarrhythmic agent according to the Vaughan Williams classification. Cardiac arrhythmias lead to sudden Death hence there is necessities to synthesize effective and safer therapeutic agents. This review highlights the chemical structure, physicochemical properties, pharmacokinetics, and antiarrhythmic activity of phenytoin with its gap analysis. Emphasis is placed on experimental models used to evaluate antiarrhythmic activity, particularly barium chloride– and adrenaline-induced arrhythmias in Wistar rats, with assessment through electrocardiogram and blood pressure measurements. Additionally, the role of oxime and amidoxime derivatives in cardiovascular therapy is discussed, given their vasorelaxation, antiplatelet, and antihypertensive properties. Molecular docking studies targeting the human cardiac sodium channel (Nav1.5) further support the potential of these compounds as sodium channel blockers. Despite its clinical usefulness, phenytoin is limited by a narrow therapeutic index, drug interactions, and toxicity. The synthesis and evaluation of novel phenytoin derivatives and oxime-based compounds may offer safer and more effective alternatives for the management of refractory ventricular arrhythmias.

KEYWORDS:- phenytoin, antiarrhythmic activity, oximes, ECG ,barium chloride.

INTRODUCTION

Phenytoin is a derivative of hydantoin, primarily utilized as an anticonvulsant medication for managing seizures.

The anticonvulsant effects of 5, 5-diphenylhydantoin (phenytoin) were discovered by Merit and Putnam in 1938. Twelve years later, it was reported that phenytoin exhibited antiarrhythmic properties in addition to its antiepileptic activities. According to Vaughan Williams' classification of antiarrhythmic agents, it falls within class Ib.[1]

Cardiovascular disorders are one of the leading causes of death, and arrhythmias contribute to almost 25% of cardiovascular-related adverse events. An irregularity in the order and/or form of electrical impulses during the cardiac cycle is referred to as an arrhythmia.[2]

Antiarrhythmic activity of phenytoin derivatives is tested against barium chloride-induced arrhythmia by taking the ECG and BP of normotensive rats.

Chemical structure, physicochemical properties

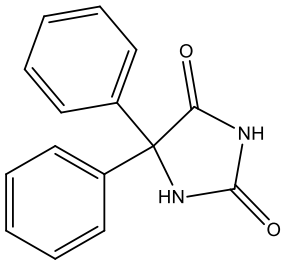


Fig.1: Structure of phenytoin.

The molecular weight of 5, 5-diphenylimidazolidine-2,4-dione is 252.273 gm/mol, and its chemical formula is $C_{15}H_{12}N_2O_2$. A compound having one imidazolidine and two benzene rings in its structure.[3]

Physical properties

Color –white powder

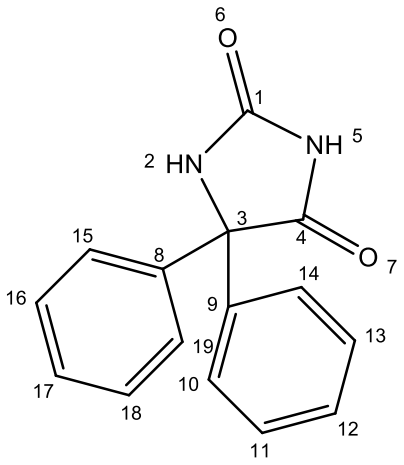
Odor – odorless

Melting point-295-298 °C

Solubility - Soluble in acetic acid; slightly soluble in ethyl ether, benzene, chloroform and insoluble in cold water Phenytoin is 90% bound to proteins and is mostly absorbed throughout the duodenum. This binding is consistent and linear for the majority of patients throughout the variety of therapies. However, several illnesses, such as hypoalbuminemia,

chronic renal failure, hepatic dysfunction, and medications, can alter binding. The primary method of phenytoin metabolism in the liver is elimination through urine.[4]

SAR of phenytoin[5]



- The hydantoin ring is essential for the activity
- Substitution at C5 usually reduces the activity
- Two phenyl rings are essential for the activity
- At least one aromatic ring is essential, but two gives the maximum activity
- Replacing one phenyl group reduces the activity
- Two carbonyl group is essential for the activity
- At least one imine group is required for activity

Synthesis of phenytoin[6]

1. Weight accurately 5.3 gm of benzil and 3 gm of urea,15 ml of aq. NaOH (30%) and 75 ml of ethanol
2. Set up the reflux condenser with RBF by using a heating mantle for at least 2 hrs.
3. Cool at room temp and then add cold water, 125ml, into the mixture
4. And then filter the mixture, take the filtrate, and add conc. HCLinto the filtrateand then immediately filter the ppt
5. Recrystallized ppt with ethanol

What are the Arrhythmias

An irregular heartbeat is called an arrhythmia. Heart arrhythmia, sometimes referred to as a heart rhythm disorder or an irregular heartbeat, is a collection of disorders in which the heartbeat is either excessively rapid or too slow.

Definition:- a group of conditions that cause irregular heartbeat or disturbance in the heart rate, heart rhythm[repetitive pattern of the heart], or both. Heartbeat may be too fast, too slow.

Causes of arrhythmia

Several factors cause an arrhythmia; they include

1. Alcohol abuse Diabetes, drug abuse, and excessive medications
2. Excessive coffee consumption, smoking, mental stress, and some dietary supplements
3. Hypertension (high blood pressure), heart disease, such as congestive heart failure
4. Hyperthyroidism (an overactive thyroid gland), Structural changes of the heart
5. Scarring of the heart, often the result of a heart attack[7]

Normal persons' healthy heart rates

Table no.1.

Normal heart rate	60 to 100 bpm[72 beats per min]
Normal blood pressure	less than (systolic)120/80(diastolic) mm Hg

Criteria for a normal heart rhythm are as follows

- Cardiac rhythm in between ranges of [60-100bpm]
- Heartbeat [impulse] must originate from the SA Node
- The cardiac impulse should propagate through the normal conduction pathway
- Normal velocity of impulse

Classification of arrhythmia[7]

Table no. 2: classification of Arrhythmia.

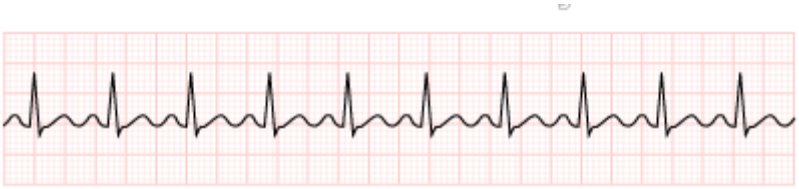
Based on the pacemaker sites			
SA node [SA arrhythmia]	**Av node & atrial musculature**	**Ventricular Arrhythmia**	**Heart block**
1. Sinus tachycardia 2. Sinus bradycardia	1. Supraventricular tachycardia 2. Atrial flutter 3. Atrial fibrillation 4. Premature atrial contraction	1. Ventricular tachycardia 2. Ventricular fibrillation 3. Premature ventricular contraction	1. SA Block 2. AV Block

1. Sinus tachycardia

It occurs when the Heart rate is above 100 bpm[fast heart rate] in the SA Node.

ECG Detection- R-R interval Distance is less

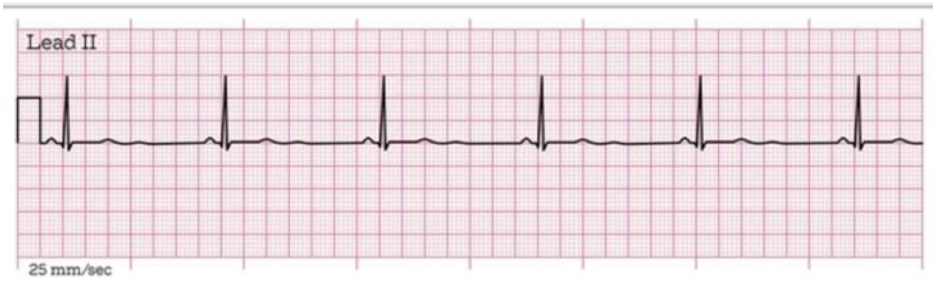
Cause-fever, during exercise, etc.



2. Sinus bradycardia

This condition occurred when the heart rate is below 60bpm [slow heart rate]in the SA node

ECG Result –p wave less formed & R-R interval distance is more.

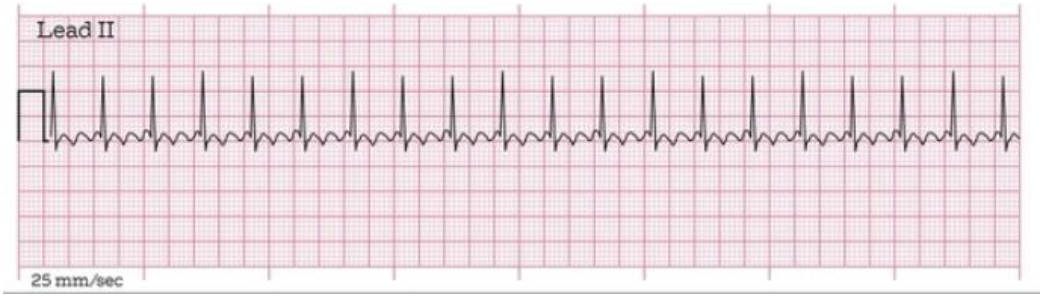


3. Atrial flutter

This condition occurs when the heart rate is between [1250-350bpm]

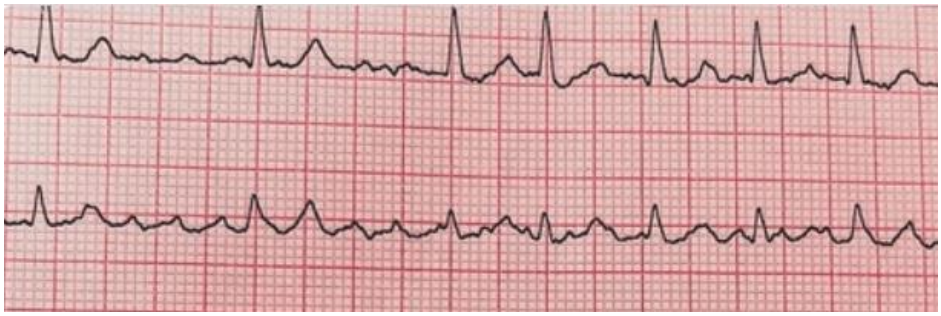
Fast heart rhythm in the atrium

ECG Detection –not defined p wave exact



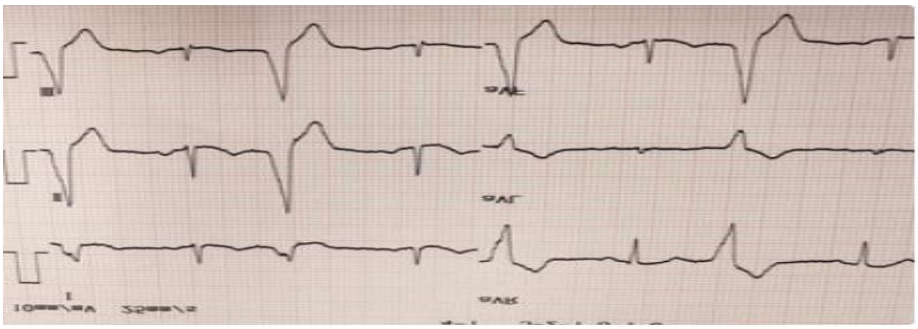
4. Atrial fibrillation

In this condition, atria beat irregularly and too fast in between [350-above]



5. Premature ventricular contraction

An ectopic beat that interrupts the normal rhythm of the heart



Vaughan Williams' classification of antiarrhythmic agents[8]

class	Blocker type	Examples
1	Sodium channel blockers	1a –procainamide, quinidine, disopyramide 1b-phenytoin, lidocaine, mexilitine 1c-flecanide,propaferanone
2	Beta blocker	Atenolol, propranolol, esmolol, metoprolol
3	Potassium channel blocker	Amiodarone, sotalol
4	Calcium channel blockers	Verapamil, diltiazem
5	others	Digoxin, atropine

Phenytoin is used as an antiarrhythmic agent

Phenytoin is used as a class 1b antiarrhythmic agent. For more than 50 years, ventricular arrhythmias have been effectively treated with phenytoin, a class IB antiarrhythmic medication. Nowadays, new drugs are getting introduced; it is still a strong medication that could be helpful in certain patients with refractory and antiarrhythmic-intolerant arrhythmia.[9]

Phenytoin is frequently used as an antiarrhythmic due to its small therapeutic window, numerous medication interactions, and side effect profile. However, it is a strong antiarrhythmic agent that may help treat ventricular tachycardia, particularly in patients who have several drug intolerances.[9]

Adverse effect of phenytoin[10]

- Hypotension
- Bradycardia
- Asystole
- QRS Widening

Role of the oximes

The oximes and amidoximes are used in the treatment of hypertension. They can relax the aorta both in vivo and in vitro. They also inhibit platelet clumping.

Hence, due to these reasons, oximes and amidoximes have a promising future used against cardiovascular diseases.[11]

The studies show that oximes exhibit in the Z/E Forms. The Z isomers are more stable than the E isomers.[12]

Molecular docking

Molecular docking studies were performed by using the Docking software for the human cardiac sodium channel Nav1.5 (PDB ID: 8F6P) to investigate the binding interactions of potential sodium channel blockers.[12]

Gap analysis

- Mexiletine is a class 1b antiarrhythmic agent, but it shows CNS toxicity.[2]
- Phenytoin shows a narrow therapeutic index
- There is a weak prolongation of the PQ interval
- Drugs show hepatotoxicity

Antiarrhythmic activity

The hydantoin derivatives exhibit both anticonvulsant and antiarrhythmic activity, therrfore they are tested against the barium chloride-induced arrhythmia by taking the ECG and BP on anesthetized and normal rats.[13]

The hydantoin derivatives show activity in two models

1. Barium chloride induced arrhythmia
2. Adrenaline-induced arrhythmia

The experiment was carried out on the male Wistar rats[180-250 g]. The animals are exposed to a constant temperature. The animals are give pellete diet and tap water. The experimental and control groups each contain 6 animals. All procedures were carried out in accordance with the Animal Care and Use Committee Guidelines and sanctioned by the ethical committee of Jagiellonian University.[14]

1. Adrenaline-induced Arrhythmia

Rats are anesthetized with thiopental [60mg/kg, intraperitoneal], and then adrenaline is administered by i.v injections. Then the tested compounds were administered before adrenaline administration.

The criterion for the activity was inhibition of the cardiac arrhythmia with the standard group comparison.[14]

2. Barium chloride induced arrhythmia

Caudal vein through the barium chloride was injected in rats [32 mg /kg, in a volume of 1ml/kg], and the standard was administered i.v. 15 min before the arrhythmia was induced, and then, 45 min before, by the i.p. route, the tested compounds were given.[13]

The Effect on the normal ECG & BP

The electrocardiogram was carried out using the apparatus of Multicard 30, standard lead, and paper speed of 50mm/s. The ECG was recorded before and after the administration of the tested compound, 1,5,15 min following, respectively, by IV at a dose of 10 mg/kg.

The blood pressure was measured in normal rats, and the tested compounds were injected at a dose of 10 mg/kg using the apparatus Datamax.

The antiarrhythmic effects of derivatives of arylpiperazine hydantoin were evaluated in two models of arrhythmia, one produced by barium chloride and the other by adrenaline. Our earlier research revealed that different hydantoin derivatives have unique antiarrhythmic efficacy in arrhythmias caused by barium chloride.[14]

Other class 1b antiarrhythmic agents.[15]

For ex. mexiltine, tocainide, lignocaine

Most of the common toxicity is the CNS toxicity, such as ataxia, twitching, etc.

Lignocaine shows cardiotoxicity, leading to the biphasic means heart rate, bp elevated or decreased. Mexilitine shows the proarrhythmic activity. Nausea and vomiting are the common side effects.

CONCLUSION

Phenytoin is a hydantoin derivatives remain important class IB antiarrhythmic agent, particularly in refractory ventricular arrhythmias. However, limitations such as narrow

therapeutic index and toxicity can be reduced by synthesizing novel phenytoin derivatives, a safer alternative. Oximes and amidoximes are also used for cardiovascular disorders, supported by molecular docking and in vivo studies, and have promising antiarrhythmic potential and warrant further development.

REFERENCES

1. K. Kiec-Kononowicz, "Synthesis, structure and antiarrhythmic properties evaluation of new basic derivatives of 5,5-diphenylhydantoin," Eur. J. Med. Chem., Jun. 2003; 38(6): 555–566. doi: 10.1016/S0223-5234(03)00075-8.
2. M. Roselli et al., "Synthesis, antiarrhythmic activity, and toxicological evaluation of mexiletine analogues," Eur. J. Med. Chem., Oct. 2016; 121: 300–307. doi: 10.1016/j.ejmech.2016.05.046.
3. R. J. Bhor, P. M. Rathod, and P. Nikam, "Synthesis and Anti-convulsant Activity of 1-[3-(4-Aminophenyl)-3-Oxopropanoyl]- 5,5-Diphenyl imidazolidine -2,4-Dione and its Derivatives," Int. J. Pharm. Investig., Sep. 2023; 13(4): 866–874. doi: 10.5530/ijpi.13.4.109.
4. H. C. Chua, N. Venketasubramanian, H. Tjia, and S. P. Chan, "Elimination of phenytoin in toxic overdose," Clin. Neurol. Neurosurg., Mar. 2000; 102(1): 6–8. doi: 10.1016/S0303-8467(99)00074-8.
5. M. Ciechanowicz-Rutkowska et al., "Structure-Activity Relationship of Some New Anti-Arrhythmic Phenytoin Derivatives," Arch. Pharm. (Weinheim), Nov. 2000; 333(11): 357–364. doi: 10.1002/1521-4184(200011)333:11%3C357::AID-ARDP357%3E3.0.CO;2-Z.
6. A. Kadam, S. Jangam, and R. Oswal, "Application of Green Chemistry Principle in Synthesis of Phenytoin and Its Biological Evaluation as Anticonvulsant Agents," J. Chem., Jan. 2011; 8: S1. doi: 10.1155/2011/159430.
7. Dr Sumanta Mondal, "PPH 308: MEDICINAL CHEMISTRY-II_Unit: I: Anti-arrhythmic drugs," 2018; doi: 10.13140/RG.2.2.35530.00965.
8. J. Kingma, C. Simard, and B. Drolet, "Overview of Cardiac Arrhythmias and Treatment Strategies," Pharmaceuticals, Jun. 2023; 16(6): 844. doi: 10.3390/ph16060844.
9. N. Yager, K. Wang, N. Keshwani, and M. Torosoff, "Phenytoin as an effective treatment for polymorphic ventricular tachycardia due to QT prolongation in a patient with multiple drug intolerances," BMJ Case Rep., Jun. 2015; 2015: bcr2015209521, doi: 10.1136/bcr-2015-209521.

10. B. Guldiken, J. Rémi, and S. Noachtar, “Cardiovascular adverse effects of phenytoin,” J. Neurol., May 2016; 263(5): 861–870. doi: 10.1007/s00415-015-7967-1.
11. T. Sahyoun, A. Arrault, and R. Schneider, “Amidoximes and Oximes: Synthesis, Structure, and Their Key Role as NO Donors,” Molecules, Jul. 2019; 24(13): 2470. doi: 10.3390/molecules24132470.
12. M. Lenaeus, T. M. Gamal El-Din, L. Tonggu, N. Zheng, and W. A. Catterall, “Structural basis for inhibition of the cardiac sodium channel by the atypical antiarrhythmic drug ranolazine,” Nat. Cardiovasc. Res., May 2023; 2(6): 587–594. doi: 10.1038/s44161-023-00271-5.
13. A. Czopek et al., “Design, synthesis, anticonvulsant, and antiarrhythmic properties of novel N-Mannich base and amide derivatives of β-tetralinohydantoin,” Pharmacol. Rep., Oct. 2016; 68(5): 886–893. doi: 10.1016/j.pharep.2016.04.018.
14. J. Handzlik et al., “Antiarrhythmic properties of phenylpiperazine derivatives of phenytoin with α1-adrenoceptor affinities,” Bioorg. Med. Chem., Apr. 2012; 20(7): 2290–2303, doi: 10.1016/j.bmc.2012.02.009.
15. C. P. Denaro and N. L. Benowitz, “Poisoning Due to Class 1B Antiarrhythmic Drugs: Lignocaine, Mexiletine and Tocainide,” Med. Toxicol. Adverse Drug Exp., Dec. 1989; 4(6): 412–428. doi: 10.1007/BF03259923.