Antiarrhythmic Properties of Phenytoin

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Abstract

BACKGROUND: Phenytoin has long been used to treat epilepsy and for some time as an antiarrhythmic drug (AAD). It is known that the diastolic calcium leakage through dysfunctional cardiac ryanodine receptors (RyR2) is a mechanism for arrhythmias in heart failure. Recent evidence suggests that phenytoin inhibits dysfunctional RyR2, reduces the calcium leak during diastole in heart failure, and may improve cardiac systolic function. This indicates the potential for repurposing phenytoin as an AAD in patients with heart failure.

METHODS: A systematic search of MEDLINE, Embase, and the Cochrane Library databases was performed in March 2019. The search was limited to the studies published in the English language from 1946 to 2019. Studies on the antiarrhythmic effects of phenytoin in adults compared to no treatment or other AADs were included. Studies were excluded if there was insufficient clinical data regarding antiarrhythmic effects, dosing and administration of phenytoin and other ADDs. Conference abstracts, editorials, case studies and review articles were also excluded.

RESULTS: A total of 157 non-duplicate titles were screened, and 25 articles underwent full-text review. 13 studies met the inclusion criteria, representing a total of 985 patients. Phenytoin was found to be effective in treating arrhythmias associated with digitalis toxicity, and in suppressing premature ventricular contractions (PVCs). In a recent animal study, phenytoin inhibited diastolic calcium leak through dysfunctional RyR2 in failing sheep hearts and improved cardiac systolic function without affecting normal functional RyR2.

CONCLUSION: Phenytoin has an acceptable safety profile when used as an AAD. It has some utility in treating digitalis-induced arrhythmias and suppressing PVCs, however, further study is needed to determine its efficacy as an antiarrhythmic in heart failure patients given new evidence of its RyR2 stabilising properties.

TRIAL REGISTRATION NUMBER: PROSPERO database (CRD42019129125).

Background

Phenytoin was first introduced by Merritt and Putnam as an antiepileptic medication in 1938 [1]. It is a voltage-dependent sodium channel blocker, it inhibits calcium-calmodulin protein phosphorylation, and is mainly metabolized in the liver. Phenytoin has been used widely for the treatment of focal and generalized seizures. [2]

The first use of phenytoin in treating cardiac arrhythmia was published in 1958 where it was used successfully in a patient to terminate recurrent ventricular tachycardia complicating acute myocardial infarction (AMI), which was refractory to procainamide and quinidine [3]. Phenytoin is classified as a class IB AAD as it blocks sodium channels in cardiomyocytes and Purkinje fibre cell membranes [4]. It was used for many years in treating atrial and ventricular arrhythmias, however, it has not been used as an AAD in recent years due to the arrival of newer AADs.

Heart failure has a complex pathophysiology and involves various tissue level changes including calcium ion (Ca^{2+}) dynamics. Ca^{2+} leak from the sarcoplasmic reticulum (SR) through dysfunctional, phosphorylated cardiac ryanodine receptors (RyR2) decreases calcium release during cardiac systole, and plays a significant role in cardiac dysfunction, arrhythmias and remodelling in the failing heart [5]. In a recent animal study, phenytoin inhibited phosphorylated RyR2 and normalised Ca^{2+} release from the SR in cardiomyocytes in failing sheep hearts, without affecting normal functioning RyR2s. This reduced calcium leak during diastole and improved cardiac systolic function [6].

Here, we review the antiarrhythmic properties of phenytoin, and its use in treating cardiac arrhythmias in adults by evaluating available studies.

Methods

Protocol and Registration

The study protocol was registered on PROSPERO prior to study selection (CRD42019129125).

Eligibility Criteria

All clinical studies with the aim to identify antiarrhythmic efficacy of phenytoin or another AAD against phenytoin in adults were included into the study. Animal studies, case series/ case reports, research on children, studies on the antiepileptic properties of phenytoin and studies with inadequate description of cardiac effects were excluded.

Search Strategy

The defined search terms including "phenytoin, diphenylhydantoin, arrhythmia, and antiarrhythmic effects" were used in different combinations in order to find publications. Our target population was adults with arrhythmia, and the intervention was phenytoin administration. We then performed a systematic search of electronic databases to find publications in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL), published in the English language between the years 1946 and 2019. All the papers were screened independently by two review

authors (EM and SB) to identify the studies, which are appropriate to the study question. Full text of these studies was assessed independently for eligibility against the inclusion and exclusion criteria and discrepancies were resolved by consensus. (Fig. 1)

Data Collection Process

Data were collected independently by the two review authors. Data fields included study type, study year, sample size, patient clinical characteristics, types of arrhythmia, symptoms, mode and dose of AAD administration, short and long-term outcomes including arrhythmia burden, response to treatment, adverse drug reactions, hospitalization, and mortality. All disagreements were resolved by consensus.

Risk of Bias

The risk of bias was assessed independently by the two reviewer authors. We used Cochrane tool for randomised trials and the ROBINS-I tool for non-randomised studies [7] (Table 1, 2). Disagreements were resolved by consensus.

Table 1
Risk of Bias Assessment

RCTs	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Tsuchioka et al., 1986	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low-moderate risk	Low-moderate risk
Karlsson, 1975	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Lovell et al., 1971	Unclear risk	Unclear risk	Unclear risk	Moderate risk	Moderate risk	Low-Moderate risk
Kemp, 1972	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Moderate risk	Low-Moderate risk

Table 2
Risk of Bias Assessment

Observational studies	Bias due to confounding	Bias in participant selection	Bias in classification of interventions	Bias due to departures from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall bias
Epstein et al., 1987	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low-moderate risk	Low risk
Caracta et al., 1973	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Damato et al., 1970	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low-moderate risk	Moderate risk
Eddy e Singh, 1969	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk-moderate risk	Moderate risk	Low risk
Seuffert et al., 1968	Low risk	Moderate risk	Moderate risk	Moderate risk	Low-moderate risk	Moderate risk	Moderate risk	Moderate risk
Rai et al., 2019	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk
Hagerman e Hanashiro, 1981	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low-moderate risk	Low risk
Karliner, 1967	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low-moderate risk	Low risk
Bernstein, Gold et al. 1965	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Results

As the result of database search, a total of 157 non-duplicate studies were screened. After reviewing the studies against the predefined inclusion and exclusion criteria, 25 studies underwent full-text review. Subsequently, 13 clinical trials representing a total number of 985 patients met inclusion and exclusion criteria and appropriately answer the study question. Of the final 13 clinical trials, 9 studies were non-randomised clinical trials and 4 were randomised controlled clinical trials. In 4 studies phenytoin was administered intravenously, in 6 studies a combination of intravenous and oral, and in 3 studies it was given orally. The therapeutic dose in all the studies was 5–10 mg/kg/day with the targeted therapeutic level of 10–20 µg/ml. (Table 3)

Table 3
The clinical trials

Study	Number	Age	Arrhythmias	Comorbidities	Other AADs	Phenytoin dose, Serum level	Adverse effects	Outcomes
Epstein, et al. 1987 (Observational)	64	35–77	VT, VF	Coronary artery disease, CCF	Not available	Serum level 10–20 µg/ml	nystagmus, dizziness, dysarthria	Phenytoin suppressed 11% of acute inducible ventricular arrhythmias on EP study, with limited long term efficacy
Caracta, et al. 1973 (Observational)	14	34–72	No baseline arrhythmias	IHD, HTN	Digoxin, procainamide	Dose 5–10 mg/kg/day	No significant adverse events	DPH did not affect His-Purkinje conduction time (HV interval), majority of the patients demonstrated enhanced AV nodal conduction (AH interval)
Damato, et al. 1970 (Observational)	13	32–70	premature ventricular contractions (PVCs), atrial tachycardia with AV block	Atherosclerotic disease	Digoxin	Dose 250–750 mg/day	No significant adverse events	DPH enhanced AV conduction (shorten the PH interval) but did not prolong IV conduction (measured by the HQ interval)
Tsuchioka, et al. 1986, (RCT)	40	36–71	Persistent sinus bradycardia, SA block and/or sinus arrest, bradycardia with ectopic supraventricular tachyarrhythmia	Sinus node dysfunction	None	Dose 5 mg/kg/day	Depressing SN function	DPH had no effect on mean SCL, the PA, AH and HV intervals, refractory periods of the atrium, the AVN and the ventricle and mean SACT. DPH has depressant effects on the sinus node in some patients with SND
Karlsson, 1975 (RCT)	81	40–99	PVCs (unifocal or multifocal), paired PVCs, R on T type ventricular ectopic beats, VT, and VF	CCF, HTN, IHD	Digoxin Procainamide	Dose 5 mg/kg/day	Hypotension, nausea, vomiting, vertigo, junctional rhythm and bradyarrhythmia	Study showed the overall superiority of procainamide over phenytoin as an antiarrhythmic drug in short-term therapy after acute myocardial infarction

Table 3. The clinical trials

Study	Number	Age	Arrhythmias	Comorbidities	Other AADs	Phenytoin dose, Serum level	Adverse effects	Outcomes
Karliner 1967 (Observational)	54	42-89	Atrial tachycardia, atrial fibrillation, Ventricular bigeminy, SVTs, VT, mostly digitalis induced	No significant cardiac backgrounds	Digoxin	Dose 300 mg/day	Hypotension, 1 death which was probably causally related to DPH	Study showed the usefulness of DPH in a variety of cardiac Arrhythmias, especially those related to digitalis toxicity
Eddy and Singh 1969 (Observational)	37	1-72	Atrial fibrillation, SVT, PVCs, Ventricular bigeminy, VT, and VF	AMI, Rheumatic heart disease, congenital heart disease, IHD, myocarditis	Digoxin, lignocaine, Procainamide, propranolol	Dose 5 mg/kg/day	Transient hypotension	Phenytoin was useful in correcting arrhythmias which are unrelated to digitalis toxicity
Seuffert, Helfant et al. 1968 (Observational)	27	22-56	PVCs, ventricular bigeminy, VT	No significant cardiac background	None	Dose 5 mg/kg/day	Transient hypotension	Phenytoin was useful in treating arrhythmias which persist during anaesthesia
Kepm, 1972 (RCT)	10	32-68	PVCs	IHD, HTN	None	Dose 300-400 mg/day	Mild sedation	DPH showed a marked reduction in the number of PVCs compared with the control group
Rai. et al. 2019 (Observational)	7	14-27	VT	Andersen-Tawil syndrome	Propranolol, verapamil, flecanide	Dose 5 mg/kg/day	No significant adverse effects	Phenytoin sodium successfully reduced the ectopic burden to <1% in 2 siblings and to <10% in the third

Table 3. The clinical trials

Study	Number	Age	Arrhythmias	Comorbidities	Other AADs	Phenytoin dose, serum level	Adverse effects	Outcome
Hagerman and Hanashiro 1981 (Observational)	10	20-47	First degree AVB, intraventricular conduction delay	No significant cardiac background	None	Dose 5-7 mg/kg/day	Hypotension	Phenytoin was effective in treatment of severe tricyclic antidepressant poisoning
Lovell et al. 1971 (RCT)	568	32-70	PVCs	IHD	None	Dose 300-400 mg/day	Rash, tiredness, ataxia	Phenytoin did not improve one-year survival rate compared to the control group. It was potentially effective in improving palpitations and irregular heart rhythms
Bernstein, Gold et al. 1965 (Observational)	60	NA	PVCs, Paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, atrial flutter	Coronary artery disease, Cerebrovascular disease	Quinidine, procainamide, digoxin	Dose 300 mg/day	Urticaria, pruritus, arthralgia, depression, drowsiness, gingival hypertrophy	Phenytoin was effective in maintaining SR in the majority of patients over a 16 months follow up period

These studies suggest that phenytoin is an effective antiarrhythmic medication in treating arrhythmias (especially in drug induced ventricular arrhythmias), with an acceptable side effect profile.

Clinical Trials

Studies of Electrophysiological Effects of Phenytoin

Epstein et al. [8] studied the efficacy of phenytoin in treating inducible ventricular arrhythmia. 64 adults with refractory ventricular arrhythmias who had failed on average 3 AADs were included in this trial. All participants underwent a baseline electrophysiology study (EPS), followed by a repeat study after administration of an AAD. They all had inducible ventricular arrhythmia (VT, VF) while receiving no AADs. Phenytoin was administered both orally (PO) and intravenously (IV) and phenytoin serum level in both responder and non-responder groups were within the therapeutic limits at the time of EPS (19.5 ± 4.7 µg/ml and 18.2 ± 4.8 µg/ml, respectively). Of the total 64 participants, only 11% of the patients had a negative EPS (responders: no inducible arrhythmias after phenytoin administration) and 89% had a positive EPS after phenytoin administration (non-responders). The responder group continued on maintenance phenytoin and non-responders were divided in 2 sub-groups to either receive AADs other than phenytoin or phenytoin either alone or in combination with other AADs. After a total of 3 years follow up, it was shown that the long-term success was limited in the responder group. Only 3% of the study participants had responded to phenytoin therapy in both initial study and long-term follow up. In the non-responder group, long-term use of phenytoin either alone or combined with another AAD was shown to be ineffective. There was 71% (5 of the 7) mortality rate in the responders to the phenytoin therapy, but only 2 of 5 deaths were due to an arrhythmia, and the authors concluded that no death in this group could be attributed directly to phenytoin failure. This trial showed that phenytoin is not an effective AAD for treating ventricular arrhythmias as assessed by suppressing inducible ventricular arrhythmias at EPS. However, most of the patients included in this study had ventricular arrhythmias that were refractory to 3 AADs and therefore the outcomes might not be representative of patients in different clinical settings.

Caracta et al. [9] investigated the electrophysiological properties of diphenylhydantoin (DPH) in 14 patients. All patients underwent a baseline EPS and a repeat study 10 minutes after phenytoin infusion. His bundle recording was used and correlated with the phenytoin blood levels to determine the impacts of DPH on the atrial, AV nodal, and His-Purkinje system refractory periods. AH interval represented the AV nodal conduction time (the onset of the low atrial depolarization to the onset of the His deflection), and HV interval represented the His-Purkinje conduction time (the onset of the His deflection to the onset of ventricular depolarization). The patients received IV DPH (5–10 mg/kg, 100 mg/5 minutes). They concluded that DPH had no effect on His-Purkinje conduction time (HV interval) in both sinus rhythm (SR) and during a variety of paced atrial rates but the

majority of patients (7 out of 14 in SR and 10 out of 14 during atrial pacing) demonstrated enhanced AV nodal conduction (AH interval) following the drug administration.

In another similar study by Damato et al. [10], 13 patients underwent EPS to identify the impacts of DPH on atrioventricular (PH interval) and intraventricular conduction (HQ interval) over different paced heart rates (HRs). They also assessed the efficacy of DPH in treating existing arrhythmias in the study participants (PVCs and atrial tachycardia). All patients in this study were on maintenance digitalis treatment. Phenytoin was administered IV in all patients (dose 250–750 mg) to either terminate the arrhythmia or reach the maximum dose of 1000 mg. There were no serious side effects requiring alteration of the treatment. DPH was found to be effective in reducing burden of PVCs. It also enhanced AV conduction (shorten the PH interval) over various paced HRs in the majority of patients but did not affect intraventricular conduction time.

Tsuchioka et al. [11], investigated the electrophysiological effects of DPH in a randomized controlled trial. They compared the effects of intravenous DPH in 20 patients who had sinus node (SN) dysfunction with 20 patients without SN dysfunction. SN dysfunction was defined as persistent sinus bradycardia, documented episodes of sino-atrial block and/or sinus arrest, and bradycardia with ectopic supraventricular tachyarrhythmia (SVTs). All the participants underwent EPS both before and after phenytoin administration (DPH, 5 mg/kg, maximum 250 mg/10 min). The PA (interval from the pacing spike to the A wave), AH and HV intervals were measured both during baseline rhythm and atrial pacing. There were no statistically significant changes in either group, in the PA, AH and HV intervals, nor in atrial, AV nodal and ventricular refractory periods, after DPH administration. DPH had also no effect on mean SCL (Sinus Cycle Length) and mean SACT (Sinoatrial conduction time) in the two groups.

Studies of Phenytoin Efficacy compared with other AADs/Placebo

Karlson et al.[12], compared the antiarrhythmic efficacy of phenytoin with procainamide. They enrolled 81 inpatients following acute myocardial infarction (AMI), who developed ventricular arrhythmia within the first 8 hours of their hospital stay. 42 patients were randomized to receive procainamide and 39 patients to receive phenytoin. Phenytoin was administered IV followed by oral maintenance dose (5 mg/kg/day). The treatment was stopped in 4 patients in each group due to either adverse effects or therapeutic failure and they were excluded from the study. There were 9 hospital deaths (5 in procainamide and 4 in phenytoin group) but only 1 of them occurred during the study period (in the procainamide group). The treatment failure rate during the first 2 hours of medication administration was higher in the phenytoin group (66%) compared to the procainamide group (34%) (P < 0.05). It was concluded that procainamide is a more effective AAD compared to phenytoin, in treating early-onset, ventricular arrhythmias complicating AMI.

The efficacy of phenytoin in treating cardiac arrhythmias was investigated in another study by Eddy et al. [13]. 37 patients (30 adults and 7 children) with acute onset arrhythmias of less than 2 days duration were enrolled in the study. 21 patients were being treated for AMI, 2 with rheumatic heart disease, 7 with congenital heart disease, 1 with ischemic heart disease, 1 with myocarditis, and 5 without any other known cardiac pathology. Other AADs such as lignocaine, procainamide, and propranolol had been tried unsuccessfully on some patients with ventricular arrhythmias. Phenytoin was given both IV and orally (5 mg/kg/day), and it was effective in treating 18 of the 21 cases with a variety of post AMI arrhythmias including SVTs (restoring sinus rhythm (SR) in 6 of 9 patients), ventricular arrhythmias (restoring SR in 10 of 12 patients) and reducing the burden of PVCs. In the other 16 patients with arrhythmias due to various causes, only 6 patients had a satisfactory response. Of the 5 patients who received oral phenytoin, 3 responded favourably. In the responders to IV phenytoin, the arrhythmias terminated in the first 10 minutes of infusion. The authors concluded that phenytoin is effective in treating ischaemic-induced arrhythmias, including in some patients that were refractory to other AADs such as lignocaine.

Kemp et al. [14] investigated the efficacy of DPH in treating non-digitalis-induced ventricular ectopic rhythms. They enrolled 10 patients from a random group of patients with PVCs detected during 12-lead electrocardiographic tracing. None of the participants had been previously treated with digoxin. They randomized 5 patients to the treatment group (DPH initially 100 mg QID orally, followed by 100 mg TDS for maintenance) and 5 patients to the control group (received placebo). It was reported that the number of PVCs in the DPH group was significantly reduced compared to the placebo group, throughout the three months study period. There was also some inconsistent reduction in the frequency of PVCs in the control group. The small number of patients enrolled in the study, the method of detecting PVCs and unclear randomization process without blinding, raises concerns about the reliability of the findings in this study.

In a study by Bernstein et al. [15] the efficacy of oral DPH was investigated in 60 patients with symptomatic recurrent cardiac arrhythmias refractory to other AADs including quinidine, procainamide and digitalis. Patients enrolled in this study had a variety of arrhythmias including paroxysmal atrial fibrillation, paroxysmal and chronic atrial flutter, premature atrial systole and PVCs. They all were commenced on DPH (300 mg/day, oral) and reviewed on fortnightly basis for an average total follow up of 16 months. The majority of the patients (62%), restored and maintained SR throughout the follow up period. DPH was discontinued in 28% of the patients due to either treatment failure or side effects. It was concluded that DPH is an effective AAD in treating recurrent cardiac arrhythmias.

Studies of Phenytoin Efficacy as a Prophylactic Antiarrhythmic Agent

Lovell et al. [16], investigated the long-term efficacy of phenytoin in treating arrhythmias after myocardial infarction and its impact on prognosis. They enrolled 568 patients admitted with AMI, 285 were randomised to receive phenytoin at non-therapeutic dose (3 or 4 mg/day), and 283 patients were randomized to receive therapeutic doses of phenytoin (300 or 400 mg/day). The patients were followed at six-weekly interval visits, for a total of 12 months. In the first 6 months, there was a lower rate of palpitations in treatment group (24%) compared to the control group (32%) (P < 0.05). This, however, might reflect a detection bias, as the visiting practitioners were not blinded. There was no difference in one-year survival rate between the two groups.

In another clinical trial, by Seuffert et al. [17], they studied the efficacy of DPH in preventing and treating arrhythmias during general anaesthesia in patients admitted for an elective inguinal hernia repair, with no previous cardiovascular comorbidities. Patients were grouped according to the anaesthetic agent used during the operation. The patients who received cyclopropane were randomized into two groups. The first group (11 patients) received IV DPH (5 mg/kg) and the second group (9 patients) received an equivalent amount of IV fluid, prior to the procedure. DPH was also given to another 10 patients who developed arrhythmias during administration of other anaesthetic agents such as halothane and methoxyflurane. There was no report of arrhythmias in 8 of the 11 patients in the treatment group throughout the entire general anaesthesia compared to only 1 of the 9 patients in the control group with no arrhythmia (P = 0.01). DPH also restored sinus rhythm in all the 10 patients who developed arrhythmia with other anaesthetic agents. This study demonstrated potential use of DPH in preventing and treating arrhythmias during general anaesthesia. However, the outcomes of this trial are based on a small number of participants in the study with no blinding in the assessment of outcomes.

Study of Phenytoin Efficacy in a rare syndrome

Rai et al. [18] in their study, investigated the efficacy of phenytoin in the rare Andersen Tawil Syndrome (ATS) which is a familial periodic paralysis affecting the heart and skeletal system. 7 siblings with the diagnosis of ATS based on cardiac arrhythmias and genetic studies were included in the study. Patients with symptomatic ventricular tachycardia or frequent PVC associated with left ventricle failure (ejection fraction < 60%) were initially treated with oral propranolol and in the event of treatment failure, underwent left sympathetic cardiac denervation (LSCD). Persistent ventricular arrhythmia (PVCs > 25%/24 hours) or ongoing symptoms despite LSCD was considered as treatment failure and managed in a stepwise approach by a trial of different medications including propranolol, flecainide, verapamil, spironolactone and nicorandil for a duration of 3–6 months per each therapy. 3 patients, who failed to respond to the previous steps, were considered for treatment with intravenous fosphenytoin followed by oral phenytoin (5mg/kg/day). After one month of phenytoin administration, the burden of PVCs reduced to < 1% /24 hours in 2 patients and < 8% /24 hours in the third patient. There was no report of significant adverse events, however, considering the small number of participants and short term follow up in this study, the long-term safety of using phenytoin in this particular group of patients could not be assessed. The authors suggested that phenytoin should only be used in ATS patients with ventricular arrhythmias or ectopic-induced left ventricular failure who are resistant to other therapies.

Studies on the Efficacy of Phenytoin in treating Drug-induced Arrhythmias

Hagerman et al. [19] enrolled 10 patients, with tricyclic antidepressant (TCA) induced arrhythmias to investigate the efficacy of intravenous phenytoin in reversal of the conduction defects. All the patients presented to the emergency department had a variety of arrhythmias including first degree AV block, intraventricular conduction delay (IVCD), and both first-degree AV block and intraventricular conduction delay in combination. Phenytoin was administered under constant ECG monitoring (5–7 mg/kg, IV, 50 mg/min, maximum dose 500 mg). All the patients achieved normalization of their conduction defect within 14 hours of phenytoin administration. The authors concluded that phenytoin is a useful drug in treating cardiac conduction defects due to TCA toxicity, however, in current clinical practice it would generally not be deemed necessary to treat asymptomatic first-degree AV block or IVCD in this setting.

Karliner et al. [20] conducted a study to identify the efficacy of phenytoin in 54 medical and surgical patients referred for management of abnormal cardiac rhythms to hospital either on the wards or in the emergency department. They were initially selected without considering prior use of digitalis or other AADs. Subsequently, 23 patients were found to have clinical suspicion for digitalis-induced arrhythmias including AF, PAT, PVCs and SVTs. DPH was administered intravenously (250 mg), with repeated dose if the arrhythmia failed to respond or recurred within two hours. This was followed by DPH maintenance therapy (100 mg TDS, PO or IMI). Success was defined as persistent restoring of SR in SVTs and recurrent ventricular tachycardia, or significant reduction of the number of PVCs. Most of the arrhythmias, especially digitalis-induced arrhythmias, responded to treatment with DPH. It was concluded that DPH is effective in treating different cardiac arrhythmias, especially arrhythmias appeared to be digitalis-induced.

Discussion

The results of this current review demonstrate the usage of phenytoin in a variety of clinical settings with a wide range of outcomes. All the studies used a similar dosage of phenytoin for treating cardiac arrhythmias. The effective dose was 5–10 mg/kg/day with the targeted phenytoin serum level of 10–20 µg/ml, which is in keeping with other data suggesting the therapeutic blood level of DPH for the treatment of most ventricular arrhythmias is generally between 10–18 µg/ml. [21]

Phenytoin is considered a safe medication with minimal hemodynamic effects in humans [22]. In clinical trials investigating the toxic effects of oral phenytoin, there was no report of cardiovascular adverse effects or serious electrocardiographic changes, and other phenytoin toxicities appeared at supra-therapeutic phenytoin serum levels (almost twofold higher than upper therapeutic level) [23, 24]. Guldiken et al. [25] published a systematic review which concluded that phenytoin is safe in both oral, and IV administration when it is given with an infusion rate of 50 mg/min and less in young patients and a rate of less than 25 mg/min in elderly patients, and that phenytoin infusion rate was more important than total dose in the development of cardiovascular adverse effects. IV administration of phenytoin with an infusion rate slower than 50mg/min was not associated with any cardiovascular mortality in 1593 patients. There is other evidence recommending an infusion rate of less than 50 mg/min to prevent cardiovascular complications including hypotension and bradycardia. [26]

In several human and animal studies, phenytoin appears to be an effective medication in treating digitalis-related arrhythmias and was proposed as the drug of choice.[27–29]

Depolarization in cardiomyocytes normally starts with the opening of the rapid sodium channels, which is followed by an increase in the intracellular sodium level. Subsequently, voltage-gated calcium channels will cause calcium entry and release of calcium from the sarcoplasmic reticulum, resulting in muscle contraction [30]. Digoxin is a cardiac glycoside, which inhibits the sodium-potassium-ATPase pump, and blocks the sodium-potassium exchange. This will allow calcium accumulation inside the cardiomyocytes by inhibiting calcium export from the myocyte via the sodium-calcium antiporter [31, 32]. The increased intracellular calcium increases contractility at therapeutic dosages and increases likelihood of after-depolarizations and arrhythmias at toxic levels. Digoxin also increases vagal activity, reduces sinus node activity, and prolongs AV nodal conduction [33]. Digitalis toxicity enhances ventricular automaticity, prolongs both atrioventricular and interventricular conduction time, and has suppressive effects on the sinus node [28]. Phenytoin is a class 1B AAD and has Na channel blocking effects [28]. It was demonstrated that DPH inhibits digitalis binding to the sodium-potassium-ATPase pump, antagonizes digitalis-induced delayed after depolarization (DAD), and also reverses the potassium efflux caused by cardiac glycosides [28, 34]. These are the likely mechanisms by which phenytoin may have reduced digitalis induced arrhythmias in the study by Karliner et al. [20].

We previously mentioned that phenytoin does not prolong interventricular conduction (HQ interval) interval and enhances AV conduction in some studies, however, its exact mechanism in shortening the AH interval is unclear [9, 10]. Bigger et al. [35] in an animal study, investigated the impacts of lidocaine on the electrophysiological properties of cardiomyocytes. It was shown that lidocaine reduced both action potential time and refractory period in Purkinje and ventricular muscle fibres and suppressed the automaticity in Purkinje fibres. These physiological properties of phenytoin and lidocaine contribute to their efficacy in treating digitalis toxicity with the electrophysiological manifestations of enhanced ventricular automaticity, prolongation of AV conduction and IV conduction [9, 36]. In contrast to these findings, studies on other AADs suggested that therapeutic doses of procainamide, quinidine and propranolol have a different effect on the IV conduction time, and almost invariably prolonged the His-Purkinje time interval both at sinus and paced atrial rates. [28, 36, 37]

In some animal and human studies, phenytoin was reported to be effective in treating TCA induced arrhythmias [19, 38]. TCAs have a "quinidine-like" effect and prolong phase 0 depolarization of the cardiac action potential in the myocardium. TCA induced cardiac conduction abnormality is due to the blockade of rapid sodium channels in the His-Purkinje system and myocardium which prolongs both repolarization and absolute refractory times. Management of TCA induced cardiotoxicity includes serum alkalinization and adjunctive treatments such as lidocaine, phenytoin, and magnesium [39]. Foianini et al. [40] in their review paper, favored using lidocaine over phenytoin in TCA cardiotoxicity. There were concerns with regards to using phenytoin due to the risk of exacerbating TCA-induced hypotension. It was also shown that lidocaine and TCAs competitively binds to sodium channels, but fast on/off kinetics of lignocaine, may potentially unbind more sodium channels. TCAs also have different kinetics in blocking sodium channels and lidocaine appeared to be more effective in treating cardiotoxicities related to TCAs with slower block to recovery time such as amitriptyline and nortriptyline [41]. In an animal study by Chopra, Laver et al. [42], it was shown that amitriptyline activates cardiac ryanodine receptors (RyR2) and causes an early release of calcium from the sarcoplasmic reticulum (SR), which may be responsible for ventricular arrhythmias. Considering phenytoin's effects in blocking dysfunctional RyR2 receptors [6], it might be effective in treating certain TCA-induced cardiotoxicities including amitriptyline. The evidence for using phenytoin in TCA-induced cardiotoxicity, however, is conflicting and additional studies are required.

We reviewed several studies demonstrating the efficacy of phenytoin in treating frequent PVCs [10, 13, 17], and its usefulness in treating arrhythmias unrelated to drug toxicity [27]. Phenytoin was also successfully used in 19 consecutive patients to suppress PVCs recorded on ambulatory ECG monitoring after surgical correction of congenital heart diseases [43]. However, it is not clear how phenytoin decreases the ventricular ectopic activity. Gupta et al.[44], in an experimental animal study reported that DPH had a direct vasodilatory effect on the coronary vessels, decreased coronary vascular resistance, and improved coronary blood flow, which could be responsible for the efficacy of DPH in improving ventricular ectopic activity (along with its Na- and RyR2 channel blocking inhibiting actions).

There are relatively few head-to-head clinical trials comparing the antiarrhythmic efficacy of phenytoin with other AADs. We previously mentioned the overall superiority of procainamide in treating post myocardial infarction arrhythmias compared with phenytoin in the study by Karlson et al. [12]. An animal experiment showed similar findings in favouring procainamide's efficacy in preventing ischaemic induced ventricular fibrillation

compared with phenytoin [45]. In the study by Bernstein et al. [15], phenytoin was effective in maintaining sinus rhythm over a 16 months follow up period in the majority patients refractory to other AADs including quinidine, procainamide and digoxin.

Tsuchioka et al. in their study [11] showed that DPH has suppressive effects on sinus node function and should be used cautiously in the treating ventricular arrhythmias in patients with sinus node dysfunction. Phenytoin was also shown in another study to have a potential effect in decreasing ventricular automaticity and the authors recommended DPH should not be used in patients with complete heart block [46].

There are conflicting data with regards to the efficacy of phenytoin as assessed by EPS. In the study by Epstein et al. [8] phenytoin had limited efficacy in treating ventricular tachycardia as assessed by EP study. Only 11% of patients responded with suppression of inducible ventricular tachycardia. Similar findings were shown in the study by Fogoros et al. [47], where the success rate of using phenytoin in suppressing inducible ventricular tachyarrhythmia was 13%. However, for the patients who had success with phenytoin, after 12-month follow up, the actuarial recurrence was 0%. These findings may suggest that the inducibility of VAs in EPS's is not a good predictor of subsequent clinical VAs in some populations or that failure of an AAD in suppressing inducible VAs during EPS's may not be indicative of their long-term efficacy.

There are little data available comparing modern AADs with phenytoin and in recent years, usage of phenytoin as an AAD has been limited to some case reports of refractory arrhythmias [48–50]. Based on new evidence from animal studies that phenytoin can stabilise Ca^{2+} leak form abnormally phosphorylated RyR2s in heart failure [6], it is worth reconsidering the use of phenytoin as an AAD.

There are some limitations to this study, which affect the strength of the evidence included in the present systematic review. There were a small number of randomised clinical trials with small number of participants applicable to the research question, and most of the studies included were outdated. Most of the RCTs were also not double blinded, controlled RCTs. The risk of bias was mild to moderate in non-randomised clinical trials and mild or unclear in randomized controlled trials reviewed in the present study.

Conclusion

Phenytoin has been shown to have low rates of cardiac toxicity when given at the doses used to treat arrhythmias. There is some evidence it is useful at treating arrhythmias in the setting of digitalis toxicity and this may be due to it inhibiting digitalis binding to the Na-K ATPase pump. It may also have some utility in treating/suppressing PVCs in limited studies reviewed here. Phenytoin has not been well studied to reduce spontaneous arrhythmias in heart failure and given recent evidence of its ability to reduce Ca^{2+} leak from phosphorylated RyR2s in this setting, further clinical studies are needed to answer this question.

Abbreviations

AADs
antiarrhythmic drugs, AEMs = antiepileptic medications AV = atrioventricular, EPS = electrophysiology study, DPH = diphenylhydantoin, PAT = paroxysmal atrial tachycardia, PVCs = premature ventricular contractions, SEs = side effects, SVT = Supraventricular tachycardia, TCAs = tricyclic antidepressants, VT = ventricular tachycardia, VF = ventricular fibrillation

Declarations

Ethical approval

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Consent for publication

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Availability of supporting data

All the supporting data are attached to the end of this papaer

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Authors' contribution

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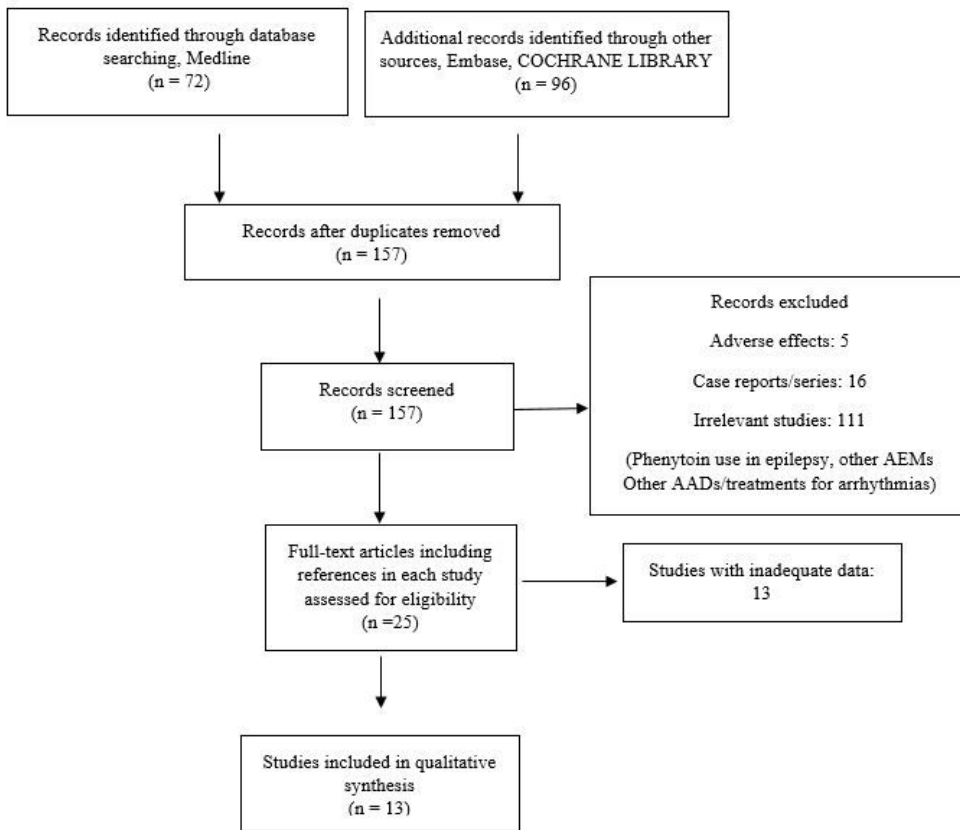
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Figure 1

Study flow diagram

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