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A Review of Structure Activity Relationship of Amiodarone and Its Derivatives

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Abstract

Structure Activity Relationship forms the basis of Rational Drug Design in the circles of pharmaceutical and medicinal chemistry. Appropriate knowledge of functional outcomes of structural modifications is crucial in conferring desired pharmacological properties to a chemical compound. Amiodarone is a classical antiarrythmic agent with a long list of adverse effects. This article attempts to review the structure activity relationship of some of the homologues of amiodarone in order to determine the most clinically desirable molecule.

Keywords

Amiodarone, Dronedarone, Structure-Activity-Relationship

1. Introduction

Structural modifications are made in a molecule and compounds are substituted to either improve their pharmacokinetic profile or to enhance their receptor affinity in order to increase pharmacological response. Insertions of certain functional groups to specific positions in a molecule result in specific outcomes. In order to properly quantify these outcomes in terms of pharmacological behavior, detailed SAR studies are vital in determination of a desired compound with ideal properties. Cimetidine, the prototypical histamine-2 receptor antagonist was the first "rationally designed" drug in which particular functional group substitutions were made on the basis of the knowledge of the target receptor to create a pharmacologically active compound [1].

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Amiodarone

Amiodarone is an antiarrythmic agent discovered in 1962 commonly used for cardiac dysrythmias. Singh and Williams (1970) accounted for its anti-anginal properties [2] while the clinical proof of its efficacy in supraventricular and ventrical arrhythmias was given by Rosenbaum *et al.*, in 1976 [3]. It is currently indicated in ventricular tachycardia, ventricular fibrillation [4] and atrial fibrillation following an open heart surgery [5]. Despite its unmatched efficacy, the use of Amiodarone is associated with a long list of adverse effects, some being fatal such as pulmonary fibrosis. Most of its ADR's are dose- and duration-dependant however, a few are idiosyncratic. Naccarelli *et al.* (1986) presented a detailed account of ADR's of Amiodarone ranging from ophthalmic, dermatological, gastrointestinal, thyroid, cardiovascular, neurological, teratogenic, hepatic and pulmonary toxicities [6].

2. Mechanism of Action

Amiodarone's action can be divided into acute and chronic phases. In acute phase, Amiodarone exerts its effects by blocking inward Sodium and Calcium currents suppressing excitability of cardiomyocytes. It also blocks ligand and voltage gated Potassium channels. In chronic phase, mediated also by its exceptionally long half-lived active metabolite, desethylamiodarone, it causes down-regulation of Kv1.5 mRNA resulting in a drug-induced modulation in gene-expression of potassium-channels [7].

3. Chemistry

Amiodarone is a benzofurane derivative with a chemical formula of (2-{4-[(2-butyl-1-benzofuran-3-yl) carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine. Its structure can be divided into 3 portions, a butylbenzofuran moiety linked with a carbonyl group to a diiodobenzene moiety linked by an ether bridge to a tertiary ethylamine as shown in **Figure 1** [8].

4. Structure-Activity Relationship

N-dealkylated metabolite of Amiodarone, Mono-Desethylamiodarone (MDEA), shows similar pharmacological profile but has a potential for greater toxicity [8]. It contains a secondary amine at the terminal end instead of a tertiary amine as shown in **Figure 2**.

Dronedarone, another clinically available analogue of Amiodarone, shares the basic benzofuran ring which is substituted by a methylsulphonamide. It also differs in the N-alkyl chain length. A prominent difference is the absence of Iodine atoms in the central benzene ring [9]. Dronedarone has generic name Multaq marketed by a multinational Sanofi Aventis Company, Paris, France. Chemically, dronedarone is proved to be effective for pharmacologic cardioversion. In clinical trials, dronedarone was set up to be superior to amiodarone in terms of having a comparatively faster and short half-life, reduced lipophilicity, and insignificant non-cardiovascular toxicity. Dronedarone has a molecular formula C31H44N2O5S with molecular mass of 556.758 g/mol. The chemical name of dronedarone is N-(2-Butyl-3-(p-(3(dibutylamino)propoxy)benzoyl)-5 benzofuranyl) methanesulfonamide (**Figure 3**) [10]. The similarity of Amiodarone with triiodothyronine (**Figure 4**) is the basis for hypo- and hyperthyroid disorders associated with its use [6].

The intention behind the replacement of iodine group is to reduce the risk of non-target organ adverse effects

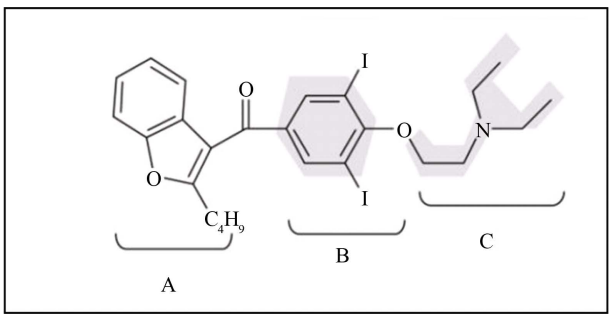

Figure 1. Amiodarone.

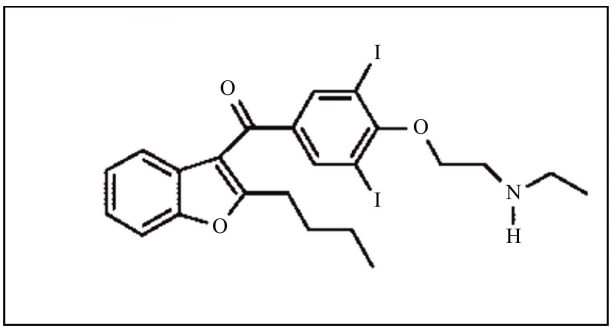

Figure 2. MDEA.

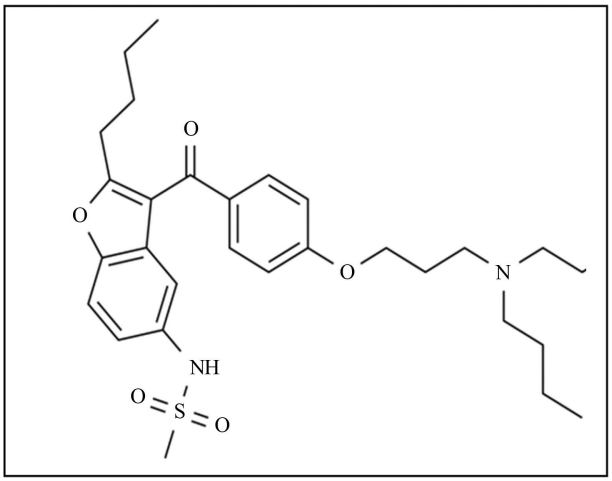

Figure 3. Dronedarone.

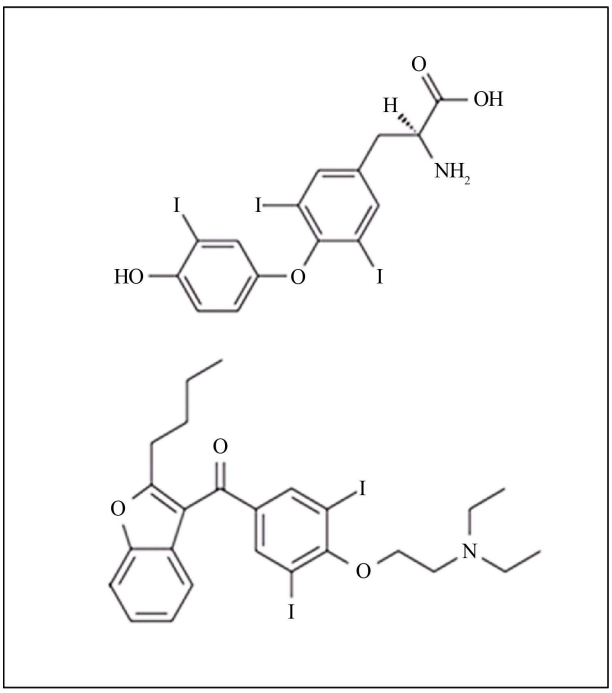

Figure 4. Top: Triiodothyronine; Bottom: Amiodarone. Note the structural similarity of the central diiodobenzene ring.

caused by amiodarone therapy and the presence of methylsulphonamide entity reduces lipophilicity, thus decreases the risks of neurotoxicity and shortens the dronedarone's half-life significantly 10. Zimalbaum (2009) compared the structural and functional characteristics of Amiodarone and Dronedarone shown in **Table 1**. Lipophilicity of Dronedarone is less than amiodarone. It has very small volume of distribution. The exclusion half-life (t1/2) of dronedarone is fairly smaller (13 - 19 h) in comparison to half-life of amiodarone which is numerous weeks. The dose of dronedarone may be less complex than amiodarone due to the pharmacokinetic profile (**Table 2**).

While exhibiting a much better ADR profile than amiodarone, dronedarone was associated with an increased risk of mortality [12] due to heart failure during clinical trials specially, among patients with reduced left-ventricular function apparently causing several deaths, ending the trial prematurely. Also, in 2011, FDA reported an apparent link between dronedarone and acute liver failure [13]. In order to overcome the problem of long elimination half-life of amiodarone, several structural modifications have also been made most noticeably by Morey *et al.*, in 2001. Introduction of methyl acetate entity at position 2 of the benzofurane ring replacing the butyl chain renders the drug susceptible to ester hydrolysis increasing its metabolism and decreasing half-life [14]. Ester homologue of Amiodarone is shown in **Figure 5**.

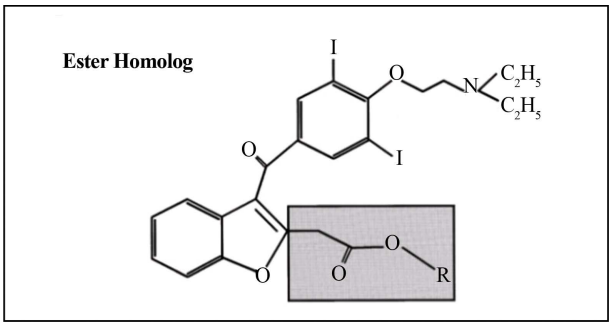

Figure 5. Ester homologue of amiodarone. The butyl side chain of benzofurane is replaced by methyl acetate.

Table 1. Structural and functional charactersistcs of dronedarone vs. amiodarone [11].

Drug	Toxic effects					Common drug interactions
	Liver	Lungs	Thyroid	Skin	Gastrointestinal tract	
Amiodarone	+	+	+	+	+	Digoxin, Warfarin
Dronedarone	-	-	-	-	++	Digoxin, Statins

Table 2. Comparison of amiodarone and dronedarone [15]-[21].

Drug	Vaughan Williams	Indication	Onset of action	Half life	Protein binding and metabolism	Route of elimination
Dronedarone	All four classes of Vaughan Williams	To decrease the chances of hospitalization in case of sudden/continual AF/AFL with current episode of AF/AFL & related CV risk factors [17]	4 - 8 h	13 - 19 h	>98% by CYP3A and CYP2D6 [23]	~renal (6%) and feces (84%) [24]
Amiodarone	All I - IV classes, but predominantly Class III	Paroxysmal supra-ventricular tachycardia (paroxysmal SVT); Recurrent ventricular fibrillation; Supra-ventricular arrhythmias; Unstable ventricular tachycardia; Recurrent supra-ventricular tachycardia; Management of acute AF and long term treatment to prevent recurrence of AF [22]	Few days to weeks (1 - 3)	40 - 55 days	>96%, by CYP3A4 and CYP2C8 [25]	Metabolized by liver & biliary excretion [26]

Table 3. Effect of ester chain elongation on half-lives of different analogues [14].

R	T1/2 (mins)
methyl	12
ethyl	6
iso-propyl	30
sec-butyl	90
neo-pentyl	240

However, this modification drastically lowers the t1/2 to 12 minutes only, making the drug useless for chronic use hence, further modifications were made in the ester side chain to make it bulkier in order to increase the steric effect for esterases and delaying inactivation. Analogues were created by adding methyl groups in the ester side chain elongating the length to form ethyl, isopropyl, sec-butyl and neo-pentyl acetates. The 5 Carbon containing neo-pentyl acetate analogues exhibited the longest half-life of 240 minutes due to increased hindrance to esterases for metabolism. **Table 3** summarizes this effect. However, in contrast to increasing half-life with elongation of ester side chain length, the increasing number of Carbon atoms also decreased the pharmacological effects with neo-pentyl acetate homologue being inactive altogether [14].

5. Discussion

Since its inception into cardiovascular medicine, Amiodarone, to date, remains a gold standard for difficult-to-treat ventricular tachycardia and fibrillation. It contains the electrophysiological properties of an ideal anti-arrhythmic agent. However, it's large volume of distribution, high tissue accumulation and exceptionally long half-life cause serious adverse effects and make it a drug of last resort. Dronedarone, a promisingly less toxic derivative caused increased mortality during trials and esterified homologues suffered activity problems. It is apparent that the benzofuran ring coupled with a benzoyl moiety is essential structural entities for activity while modifications can be made at other positions on the molecule and a safer derivative can be developed which retains most of the activity, as no other drug in this class exhibits a multi-channel blocking effect which is pharmacodynamicaly ideal for an anti-arrhythmic agent. Till then, Amiodarone remains unchallenged due to its superior clinical efficacy.

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Conflict of Interest

The authors confirm that this article content has no conflicts of interest.

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