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Editorial

Happy 50th anniversary of amiodarone (1969–2019)

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History

The discovery of amiodarone was the result of a research program initiated in the 1960s by Labaz laboratories in Belgium with the objective of developing new coronary vasodilators for the treatment of chronic angina. The starting point was the benzofuran ring of khellin, a chromone isolated from the seeds of the *Ammi visnaga*, introduced as an antianginal agent in 1945. Initially, Labaz laboratories identified two potent coronary vasodilators: benzarone and its diiodinated derivative, benzodiarone. Based on benzodiarone, Charlier et al. synthesized in 1962 another di-iodinated benzofuran derivative, amiodarone, [2-butyl-3-(3,5-diiodo-4-β-diethylaminoethoxybenzoyl)-benzofuran hydrochloride, Labaz 3428] with potent coronary vasodilator properties [1]. In 1962, β-adrenergic blockers were introduced as antianginals, but they reduce coronary blood flow at rest and exacerbate coronary artery spasm due to unopposed α-adrenergic vasomotor tone. Thus, Labaz researchers hypothesized that it would be of interest to develop a drug with a partial antagonism of α- and β-adrenergic stimulation to avoid an excessive inhibition of the sympathetic tone. They selected amiodarone because it produced a non-competitive α- and β-adrenergic antagonism [2], and the drug was commercialized in the late 1960s as an antianginal drug [3]. In 1964 the antiarrhythmic effect of β-adrenergic blockers was demonstrated, but the antiarrhythmic effects of amiodarone were not studied just because they were not expected.

Fifty years ago, in 1969, Charlier et al. demonstrated that amiodarone effectively suppressed a variety of experimental cardiac arrhythmias induced by barium chloride, acetylcholine, aconitine, strophantine or following acute coronary occlusion. However, it was unclear whether the antiarrhythmic activity of amiodarone simply reflected its sympatholytic activity or some other property was involved [4]. In 1970, Singh and Vaughan Williams demonstrated that in anesthetized guinea-pigs acute administration of amiodarone slowed the sinus rate and protected against ouabain-induced arrhythmias [5]. However, in contrast to class I antiarrhythmic drugs (AADs), like quinidine, amiodarone had no effect on electrophysiological parameters in isolated rabbit heart muscles, which was consistent with the finding that intravenous amiodarone did not modify the H—V, QRS or QT/QTc intervals in humans [6,7]. Surprisingly, pre-treatment with amiodarone for 6 weeks slightly reduced the V_{max}, but markedly lengthened the action potential duration (APD) and refractoriness in isolated rabbit atrial or ventricular muscle fibers. This lengthening was significant after the first week of treatment and progressively increased during long-term treatment, while V_{max} was significantly reduced only after 3 weeks' treatment. Thus, Singh and Vaughah Williams concluded that the antiarrhythmic effect of amiodarone was related to its ability to prolong cardiac APD and refractoriness at concentrations at which it did not modify intracardiac conduction velocity and proposed amiodarone as the first member of a new class (class III) of AADs [5].

In the 1970s, Rosenbaum et al. found amiodarone remarkably effective in the treatment and prevention of supraventricular (atrial flutter or fibrillation, Wolff-Parkinson-White syndrome) and ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation), even in patients with previous myocardial infarction, heart failure or chagasic myocarditis [8]. Nowadays, amiodarone is the AAD of choice in patients with structural heart disease (heart failure, left ventricular dysfunction, coronary artery disease, post-myocardial infarction, cardiomyopathies) where most AADs are contraindicated. As a logical consequence, amiodarone-like drugs (budiodarone, dronedarone) and many class III AADs were developed (almokalant, ambasilide, azimilide, bretylium, dofetilide, ibutilide, risotilide, sematilide, sotalol, tedisamil and others) were developed, but all these drugs failed to show the antiarrhythmic properties and efficacy of amiodarone.

Amiodarone is a multifaceted ("*dirty*") drug with multiple mechanisms of action (Supplemental Table 1) [7,9,10]:

- It inhibits the inward-depolarizing Na^+ and L-type Ca^{2+} (I_{CaL}) currents and several outward-repolarizing K^+ currents, and exerts a non-competitive α- and β-adrenergic antagonism i.e., it exhibits class I, II, III and IV antiarrhythmic actions according to the Vaughan Williams classification.
- The acute and chronic clinical electrophysiological effects of amiodarone are very different. Intravenously, its main effect is the lengthening of atrio-ventricular nodal refractoriness with minimal effects on atrial and ventricular refractoriness and QRS, H—V and QTc intervals, an effect possibly related to the blockade of I_{CaL} and the non-competitive β-adrenergic antagonism. On long-term treatment,

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amiodarone lengthens the APD in all cardiac tissues, preferentially in those with the shortest APD (His bundle, atrial muscle, ventricular epicardium/endocardium), with lesser effects in Purkinje fibers and M cells. Thus, in contrast to other class I and III AADs, amiodarone reduces transmural dispersion of repolarization. Furthermore, APD lengthening is independent of heart rate, i.e. amiodarone does not present reverse use-dependence.
- Amiodarone prolongs the QT but produces a low incidence of torsades de pointes, probably due to the inhibition of $I_{Ca,L}$, the blockade of β-adrenoceptors, the absence of reverse use-dependence and the reduction in QT dispersion of repolarization.
- In cardiac pacemaker cells, amiodarone decreases the spontaneous firing rate and suppresses abnormal automaticity and triggered activity induced by early/delayed afterdepolarizations.

Unfortunately, clinical use of amiodarone is hindered by: its extensive tissue distribution which explains the long time (weeks/months) needed to reach plasma steady-state values unless a loading dose is used; its prolonged half-life (30–100 days); the high frequency of cardiac and extra-cardiac adverse effects (its Achilles heel) leading to drug discontinuation in ~20% of patients during long-term therapy; and its multiple drug interactions.

In conclusion, in 2019 we celebrate the 50th anniversary of amiodarone, a drug with a complex mechanism of action that represents the most effective AAD for the prophylaxis and treatment of cardiac arrhythmias and a complement to non-pharmacological treatments in an attempt to win the battle against cardiac arrhythmias. Amiodarone, however, is hampered by its poor safety profile. Therefore, we will continue the search for new AADs safer and more effective AADs than those currently available. A better understanding of the pathophysiological mechanisms directly involved in the genesis/maintenance of cardiac arrhythmias (a *well-supported hypothesis*) and how they are modified by comorbidities, is the first step for the identification of new therapeutic targets and the rational design of new AADs.

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Disclosure

The author states that there are no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.080.

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