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Quinidine Therapy in Ventricular Fibrillation-Related Channellopaties: Is it Really Useful Nowadays?

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Short Communication

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Abstract

In the last three decades with the increasing evidence regarding molecular basis of channellopathies, there was an impressive interest and revival of quinidine therapy due to the unique pharmacological multichannel properties of the drug. Currently available data from observational studies and small reports suggest that quinidine may represent a potential treatment option for ventricular fibrillation either idiopathic or associated to other channellopaties. Quinidine shows a very complex profile of electrophysiological effects that is still not completely understood. The principal therapeutic action of quinidine in patients with either ventricular or atrial arrhythmias is to cause frequency-dependent increases in relative tissue refractoriness, leading to interruption of reentry. Prolongation of the ventricular effective refractory period in relation to the duration of the action potential is strongly dependent on frequency and is correlated with the suppression of ventricular tachycardia. Slowing of conduction may also contribute to the antiarrhythmic action of quinidine. This pharmacological agent remains one of the oldest cardiac drugs still available in the modern era of antiarrhythmic therapy, although not in every country. Currently, quinidine has been proved to be a live-saving antiarrhythmic drug able to control ventricular tachycardias and ventricular fibrillations in patients with channellopathies, specially the Brugada's syndrome. The therapy of VF with electrophysiologically-guided quinidine may be implemented after demonstrating that VF is no longer inducible after quinidine therapy. Drug therapy with quinidine in ICD patients is usually beneficial by reducing the frequency of appropriate shocks, which can improve the patient's quality of life. Nowadays, quinidine is not only useful in VF-related channellopathies, but it is also a lifesaving pharmacological agents in these patients. Therefore, Quinidine should be available in every hospital, in every drug store, anywhere in the world.

Keywords: Quinidine; Ventricular fibrillation; Channellopathies; Brugada syndrome

Introduction

Since quinidine was first described, the drug has been used in the treatment of almost all cardiac arrhythmias, particularly atrial fibrillation [1]. There has been a notorious decreased in clinical prescription in the last two decades mainly due to the concern of side effects such as pro-arrhythmia, leading to increased mortality, and to the availability of newer anti-arrhythmic drug agents, as well as, catheter based ablation therapy [2-5]. However, in the last three decades with the increasing evidence regarding molecular basis of channellopathies, there was an impressive interest and revival of quinidine therapy due to the unique pharmacological multichannel properties of the drug. Currently available data from observational studies and small reports suggest that quinidine may represent a potential treatment option for ventricular fibrillation either idiopathic or associated to other channellopaties [6-9].

Quinidine shows a very complex profile of electrophysiological effects that is still not completely understood. The principal therapeutic action of quinidine in patients with either ventricular or atrial arrhythmias is to cause frequency-dependent increases in relative tissue refractoriness, leading to interruption of reentry. Prolongation of the ventricular effective refractory period in relation to the duration of the action potential is strongly dependent on frequency and is correlated with the suppression of ventricular tachycardia. Slowing of conduction may also contribute to the antiarrhythmic action of quinidine [10-14]. This pharmacological agent remains one of the oldest cardiac drugs still available in the modern era of antiarrhythmic therapy, although not in every country. Quinidine is considered a Class I, membrane stabilizing antiarrhythmic agent. Quinidine decreases the phase zero of rapid depolarization of the action potential by blocking the rapid sodium channel. It is further sub-classified as Class IA drug due to its intermediate offset kinetics, namely, time constants for recovery from block. Therefore, the effect on conduction velocity is more pronounced in comparison to Class IB, but lower compared to Class IC agents.

ICD therapy is the treatment of choice for patients with both primary and secondary prevention in ventricular fibrillation-related channellopathies, with the role of antiarrhythmic therapy aimed at reducing the number of recurrences. However, implantable devices do not prevent arrhythmias, thus, patients who have frequent symptoms or device discharges from recurrent arrhythmias may benefit from adjunctive anti-arrhythmic drug therapy. Although ICD implantation is the treatment of choice in IVF patients, in this short communication, we will discuss the current role of quinidine in the therapeutic management of ventricular fibrillation in certain channellopaties.

Pharmacological and Clinical Effects of Quinidine

The alkaloid quinidine represents the D-isomer of the antimalarial drug quinine and can be derived from the bark of the cinchona tree. Quinidine sulfate or gluconate, and quinidine polygalacturonate darken when exposed to light. Therefore, these substances should be stored in well-closed, opaque containers. Solutions of quinidine salts acquire a brownish tint under impact of light [15]. Quinidine depresses the maximal upstroke velocity of the action potential due to the drug-induced inhibition of the rapid inward sodium current [16]. The extent of such upstroke slowing was greater at higher pacing frequencies, a finding that contributed to the formulation of the modulated-receptor hypothesis [17,18]. Therefore, the affinity of a channel-associated receptor for a certain drug is modulated by the state of the channel, with use-dependent blockade being a result of higher affinity for open, or inactivated, channels than for resting channels [18].

Sodium-channel blockade by quinidine follows specific, saturable binding to defined receptor sites, which are now being characterized with the use of molecular approaches [19-22]. Quinidine was found to have multi-channel blocking properties. It also inhibits many potassium channels in cardiac tissue, and clinically relevant effects are thought to be due to suppression of the repolarizing delayed rectifier current. This current has at least three distinct components, and quinidine exerts its most important effects by inhibiting the rapidly activating component, IKr [23-27]. Besides blocking the INa, quinidine reduces repolarizing K+ currents (IKr, IKs), the inward rectifier (IK1), and the transient outward current Ito [5]. Furthermore, quinidine reduces the L-type ICa and the late INa inward currents that are responsible for the plateau phase two of the action potential. Altogether these complex effects result in a prolongation

of the action potential duration that is more pronounced at slower heart rates. It is of clinical relevance that quinidine changes the morphology of the ventricular action potential to a triangular shape by shortening the plateau but prolonging the late depolarization, facilitating the formation of early after-depolarization. In addition, quinidine seems to have effects on the spatial dispersion of ventricular repolarization [5].

In patients with either congenital or acquired long-QT syndromes, impaired IKr function is strongly implicated in the development of torsade de pointes [28,29]. The ultrarapid component of the delayed rectifier potassium current is also inhibited at therapeutic concentrations of quinidine; this may have a role in the beneficial effects of this Class I drug agent [25]. The quinidine-induced blockade of delayed rectifier potassium channels, like that of sodium channels, is attributable to binding at a site within the inner pore of the channel [30,31]. Binding to this receptor is also modulated with respect to time and voltage. However, because the "reverse use dependence" effect, at slow rates, there is often greater receptor occupancy in the potassium channel than in the sodium channel, and repolarization is consequently prolonged [32-34]. The precise mechanisms underlying this phenomenon are uncertain, but enhanced receptor binding of quinidine may occur when the heart rate is low as a result of reduced accumulation of extracellular potassium [33-35].

Available therapy for VF patients may include ICD implantation, drug therapy, radiofrequency catheter ablation of the triggering focus or combinations of the above. Secondary and primary prevention trials have demonstrated the superiority of ICD compared with antiarrhythmic medication in preventing death. ICD therapy is the treatment of choice for patients with both primary and secondary prevention with the role of antiarrhythmic therapy aimed at reducing the number of recurrences. Implantable devices do not prevent arrhythmias, thus, patients who have frequent symptoms or device discharges from recurrent arrhythmias may benefit from adjunctive anti-arrhythmic drug therapy with quinidine. This drug agent shows a very complex profile of electrophysiological effects that is still not completely understood. The principal therapeutic action of quinidine in patients with either ventricular or atrial arrhythmias is to cause frequency-dependent increases in relative tissue refractoriness, leading to interruption of reentry [19-20]. Prolongation of the ventricular effective refractory period in relation to the duration of the action potential is strongly dependent on frequency and is correlated with the suppression of ventricular tachycardia [36]. Slowing of conduction may also contribute to the antiarrhythmic action of quinidine. Moreover, quinidine impairs impulse conduction across ischemic gaps, and Purkinje system-muscle junctions, suggesting further contributing mechanisms to the interruption of reentry in pathological tissue with electrophysiological alterations [37-40].

Due to quinidine´s complex cellular effects, it provides a wide range of activity influencing both reentrant as well as ectopic supraventricular and ventricular arrhythmias. The therapeutic effects are probably based on the prolonged effective refractory period and increased action potential duration in atrial and ventricular cells and in the His-Purkinje system. It is relevant that the affected cardiac tissue remains refractory even after restoration of the resting membrane potential because the prolongation of the effective refractory period is greater than the increase in the duration of the action potential [41,42]. In normal clinical doses, quinidine decreases the automaticity in the sinus node, the His-Purkinje system and ectopic pacemakers. However, the clinical effect also depends on the anticholinergic and hemodynamic impact. In the fast AV nodal pathway as well as in accessory pathways, quinidine slows conduction and increases refractoriness [43]. In standard 12-lead ECG, quinidine increases sinus rate due to the vagolytic effect and prolongs the duration of the QRS complex, as well as, the QTc interval with no or little prolonging effect on the PR interval [43].

Nowadays, there has been an awakening in the utilization of Quinidine in other clinical settings. In the last three decades with the increasing evidence regarding molecular basis of the channellopathies, there has been a revival of quinidine therapy due to the unique pharmacological multichannel properties of this Class I agent. Among the channellopathies, the J Wave Syndromes raised particular interest and research efforts, being the Brugada Syndrome and the Early Repolarization Syndrome the two manifestations of the J Wave Syndromes [44-48]. The J wave syndromes are associated with predisposition to development of polymorphic VT and ventricular fibrillation leading to sudden cardiac death in young adults without apparent structural heart disease [49-53]. Recent guidelines and expert consensus recommend quinidine therapy in particular conditions in several life-threatening congenital arrhythmogenic syndromes [54,55]. There are observations that support the notion that IVF has a focal origin. It was demonstrated that IVF represents a "focal VF" triggered by ectopic beats originating from Purkinje fibers [39]. These Purkinje

premature ventricular contractions are so premature that fall on the vulnerable period of the surrounding ventricular tissue, initiating reentrant VF. Belhassen B, et al. [51] investigated quinidine drug therapy during electrophysiological studies in a population of patients with IVF and inducible ventricular tachycardia or fibrillation. This pharmacological therapy was able to prevent the re-induction in 96% of patients. A reentrant or triggered mechanism seems to play a role in these patients who had a high percentage of inducible ventricular arrhythmias during electrophysiological study. Currently, therapy with quinidine can be considered in this kind of patients with IVF with a Class IIb indication [55]. The production of Quinidine was partially discontinued in 2006. Viskin S, et al. [56-58] documented in a nicely done manuscript that quinidine was inaccessible or available only with delay in 86% of 130 countries surveyed in 2013. Viskin S, et al. reported 22 patients experiencing potentially life-threatening arrhythmias attributable to the unavailability of quinidine. This very old pharmacological drug agent represents in the modern era of drug therapy until now an irreplaceable life saving antiarrhythmic medication in patients with channellopathies associated to ventricular fibrillation.

Conclusion

In conclusion, although more than three decades ago quinidine was still one of the most utilized antiarrhythmic agents, it was progressively abandoned. Currently, quinidine has been proved to be a live-saving antiarrhythmic drug able to control ventricular tachycardias and ventricular fibrillations in patients with channellopathies, specially the Brugada's syndrome. The therapy of VF with electrophysiologically-guided quinidine may be implemented after demonstrating that VF is no longer inducible after quinidine therapy. Drug therapy with quinidine in ICD patients is usually beneficial by reducing the frequency of appropriate shocks, which can improve the patient's quality of life. Nowadays, quinidine is not only useful in VF-related channellopathies, but it is also a life saving pharmacological agents in these patients. Therefore, Quinidine should be available in every hospital, in every drug store, anywhere in the world.

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