Quinidine in Brugada Syndrome

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QUINIDINE

Quinidine is a Class IA antiarrhythmic drug –isomer of quinine found in the bark of the cinchona tree. The drug affects depolarization and repolarization by blocking Na^+ and K^+ channels respectively. The rapid Na^+ channel block accounts of its greater effect on depressing V_{max} at faster rates.
In the Brugada disease it is used by its property to block the Ito channel and thus restorer electrical homogeneity across ventricular myocardial wall and in abolishing arrhythmias by phase 2 reentry. Quinidine, by virtue of its actions to block I(to), has been proposed as adjunctive therapy, with an implantable cardioverter defibrillator as backup. Additionally the drug has a benefic vagolytic effects occur through muscarinic (M_2) receptor block.

Channels and receptors block by Quinidine

Fast Na^+ current; I_{to1} channel or transient outward current; Inward rectifier I_{K1}, delayed rectifier: I_{KS}, I_{KR} and I_{KUR}, I K_{ATP} or adenosine triphosphate ATP sensitive potassium channel, $IK_{\text{-Ach}}$, lpha 1 and alpha 2 adrenergic receptors: can cause orthostatic hypotension and reflex sinus tachycardia; M_2 muscarinic receptor.

Pharmacokinetics

Bioavailability: 70% to 85%;
Protein binding: 70% to 95% with alpha 1 Glicoprotein;
Time to Peak Concentration: 1h to 4h;
Elimination $T_{1/2}$: 6h o 8h;
Therapeutic Range 2 to 5 micrograms/ml;
Elimination Route: hepatic through the cytochrome P450 system.

Effects on ECG and Electrophysiological intervals

SCL: > or 0;
PR interval: 0;
QRS interval > +;
QT/QTc interval: > ++;
JT interval: > ++;
AH interval: <+;
HV interval: >+;
Atrium Effective Refractory Period: >+;

Atrioventricular Node Effective Refractory Period: >+;
His-Purkinje system Effective Refractory Period: > +;
Ventricle Effective Refractory Period: >+;
Accessory Pathway Effective Refractory Period

In 1987, Imaizumi et al **(Imaizumi Y, Giles WR. Quinidine –induced inhibition of transient outward current in cardiac muscle. Am J Physiol 1987; 253:H704-H708.)** showed that quinidine induced inhibition of transient potassium outward current, potassium initial outflow ("transient outward current"), or "4-aminopyridine sensitive outward current" in cardiac muscle**.**

Yatani et al **(Yatani A, Wakamori M, Mikala G, et al. Block of transient outward type cloned cardiac K+ channel current by quinidine. Circ Res 1993; 73:351-359.)** cloned cardiac K+ channel transient outward type by quinidine**.**

Research from the Masonic Medical Research Laboratory has suggested a new pharmacological approach to therapy using "transient outward current" blockers. This pharmacologic alternative may be critically important in many parts of the world where ICDs are not affordable (**Antzelevitch C, Yan GX, Shimizy W, Burashnikov A. Electrical Heterogeneity, the ECG, and Cardiac Arrhythmias. In. Zipes DP, Jalife J. Cardiac Electrophysiology From Cell to Bedside third Edition W.B. Saunders Company. 2000; Chapter 26 pp 222-238.).**
Additionally, this is particularly important because Brugada patients are at risk of SCD since the age of 6-month-old **(Suzuki H, Torigoe K, Numata O, Yazaki S.Infant case with a malignant form of Brugada syndrome.J Cardiovasc Electrophysiol. 2000;11:1277-1280.)**, and ICD implant is not feasible in very young children **(Gaita F, Giustetto C, Bianchi F, et al. Short QT syndrome: pharmacological treatment. J Am Coll Cardiol. 2004;43(8):1494-1499.)** Belhanssen et al **(Belhassen B, Viskin S, Fish R, et al. Effects of electrophysiologic-guided therapy with Class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol. 1999;10:1301-1312.)** performed EP studies in 34 consecutive patients who had IVF with (n = 5) or without (n = 29) the BrS. All patients with inducible SPVT/VF underwent repeated EP evaluation after oral administration of quinidine.
Patients rendered noninducible received this therapy on a long-term basis. SPVT/VF were induced in 27 (79.4%) patients at baseline studies. Quinidine effectively prevented induction of SPVT/VF in 26 (96%) patients. Of the 23

patients treated with these medications, no patient died or had a SVT during a mean follow-up period of 9.1 +/- 5.6 years (7 to 20 years in 15 patients). Two deaths occurred in patients without inducible SPVT/VF at baseline studies who had been treated empirically. Its results suggest that EP-guided therapy with quinidine is a reasonable, safe, and effective approach for the long-term management of it patients. Publications have shown a decrease or disappearance of ST elevation in right precordial leads with administration of quinidine by decreasing in the initial outflow of potassium through the Ito channel **(Chen PS. What's new in EP: Quinidine is good but fever is bad for Brugada syndrome. J Cardiovasc Electrophysiol 2000; 11:1265.) (Alings M, Dekker L, Sadee A, Wilde A. Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. Pacing Clin Electrophysiol 2001;24: 1420-1422.)** .
The drug reduces the magnitude of the Ito channel – mediator of phase 1 and consequently normalize the elevation of the ST segment in BrS.
Additionally, it could improve repolarization due to its vagolytic effect (M_2 muscarinic receptor block) and to the exacerbation of reflex sympathetic tone.
At a dose of 1000mg **(Mok NS, Chan NY, Chi-Suen Chiu A. Successful Use of Quinidine in Treatment of Electrical Storm in Brugada Syndrome.Pacing Clin Electrophysiol. 2004; 27:821-823.)** to 1500mg/day oral (300mg every 6 hours) quinidine bisulphate can be successful for suppress the electrical storm.
The drug also normalize the ST-segment elevation in right precordial leads, suppress all ambient unifocal PVCs and induction of VF on PES.
Hydroquinidine therapy prevented VT/VF inducibility in 76% of asymptomatic patients with BrS inducible arrhythmia, as well as VT/VF recurrence in all BrS patients with multiple ICD shocks.
These preliminary data suggest that preventive treatment with it drug may be an alternative strategy to ICD placement in asymptomatic patients with BrS and inducible arrhythmia **(Hermida JS, Denjoy I, Clerc J, et al.Hydroquinidine therapy in Brugada syndrome. J Am Coll Cardiol. 2004; 43: 1853-1860.).**
Management of patients with BrS is still far from being well defined.
Interestingly in some reports, hydroquinidine has been found to reduce the incidence of ventricular arrhythmia in the follow-up as well as the rate of ventricular arrhythmia induction in the EP lab. Yet, prophylactic ICD implantation remains the treatment of choice in symptomatic and inducible patients. **(Anselme F, Frank R. The best of arrhythmia in 2004 Arch Mal Coeur Vaiss. 2005; 98 Spec No 1:57-62.).**
After arrhythmic storm quinidine could be effective to stop these new omiosus events (**Marquez MF, Rivera J, Hermosillo AG, et al. Arrhythmic storm responsive to quinidine in a patient with brugada syndrome and**

vasovagal syncope. Pacing Clin Electrophysiol. 2005;28:870-873.). Schweizer et al (.(**Schweizer PA, Becker R, Katus HA, Thomas D. Successful acute and long-term management of electrical storm in Brugada syndrome using orciprenaline and quinine/quinidine. Clin Res Cardiol. 2010 Jul;99:467-470**.) present a case with successful acute and long-term management of electrical storm in BrS using orciprenaline and quinidina. Mehrotra et al (**Mehrotra S, Juneja R, Naik N, Pavri BB. Successful Use of Quinine in the Treatment of Electrical Storm in a Child with Brugada Syndrome. J Cardiovasc Electrophysiol. 2010 Oct 6. doi: 10.1111/j.1540-8167.2010.01907**.) related a case of a 10-year-old girl developed life-threatening recurrent PVT following surgical closure of a secundum atrial septal defect successful post hoc analysis of a Holter recording suggested BrS.

After managing the acute phase, a dual chamber defibrillator was implanted. One week later she experienced VF electrical storm (ES), needing 96 appropriate shocks within a few hours. Quinidine, by virtue of its I_{to} blocking property, is the only drug reported to be useful in managing VF-ES in BrS. Non availability of quinidine led us to try its diastereomer, intravenous quinine, which succeeded in controlling the VT. ES in the setting of ion channelopathy can be difficult to manage, and sometimes requires innovative therapies. Bouzeman et al (**Bouzeman A, Traulle S, Messali A, Extramiana F, Denjoy I, Narayanan K, Marijon E, Hermida JS, Leenhardt A. Long-term follow-up of asymptomatic Brugada patients with inducible ventricular fibrillation under hydroquinidine. Europace. 2013 Sep 25. [Epub ahead of print**] evaluated the long-term efficacy and safety of an electrophysiologically guided therapy, based on a strategy of treatment using hydroquinidine (HQ) among asymptomatic Brugada patients with inducible VF. In two French reference centers, consecutive asymptomatic type 1 Brugada patients with inducible VF were treated with HQ (600 mg/day, targeting a therapeutic range between 3 and 6 μmol/L) and enrolled in a specific follow-up (mean 6.6 ± 3 years), including a second programmed ventricular stimulation (PVS) under HQ.

An ICD was eventually implanted in patients inducible under HQ, or during follow-up in case of HQ intolerance, as well as occurrence of arrhythmic events. From a total of 397 Brugada patients, 44 were enrolled (47 ± 10 years, 95% male). Of these, 34 (77%) were no more inducible (Group PVS-), and were maintained under HQ alone during a mean follow-up of 6.2 ± 3 years. In this group, an ICD was eventually implanted in 4 patients (12%), with occurrence of appropriate ICD therapies in one. Among the 10 other patients (22%), who remained inducible and received ICD (Group PVS+), none of them received appropriate therapy during a mean follow-up of 7.7 ± 2 years.

The overall annual rate of arrhythmic events was 1.04%, without any significant difference according to the result of PVS under HQ. One-third of patients experienced device-related complications. This long-term follow-up results emphasize that the rate of arrhythmic events among asymptomatic Brugada patients with inducible VF remains low over time. This results also suggest that residual inducibility under HQ is of limited value to predict events during follow-up.