Monitoring the electrophysiological effects of hydroquinidine non-invasively in patients with Brugada syndrome

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Background: Quinidine and its derivative hydroquinidine are the only drugs shown to reduce arrhythmic events in patients with Brugada syndrome (BrS). There is currently no standardised approach to monitoring the effect of pharmacotherapy in BrS to guide dosing and evaluate an individual’s response to therapy.

Purpose: To investigate if the electrophysiological effects of Hydroquinidine can be detected on non-invasive testing and identify parameters that may be used to study a non-invasive strategy for monitoring pharmacotherapy in BrS.

Methods: Patients with a diagnosis of BrS underwent multimodality non-invasive assessment with electrocardiogram (ECG), signal averaged ECG, 24 hour 12-lead Holter monitor and electrocardiographic imaging (ECGi – a method of non-invasive electroanatomical mapping), at baseline and “on treatment” with hydroquinidine (300mg BD) therapy. A medication survey was used to recorded adverse drug reactions and serum hydroquinidine levels were determined using liquid chromatography mass spectrometry.

Results: Twelve patients with BrS (11 male, mean age 47.6 ± 10.9 years) with spontaneous type 1 BrS pattern or drug inducible type 1 BrS pattern and resuscitated cardiac arrest participated in the study. The mean Shanghai score was 4.6 ± 1.4 and two patients had disease-causing SCN5A variants. During hydroquinidine therapy, there was a significant increase in QRS duration (110.7msec vs 117.8msec, p=0.004) and in mean activation time in the area of late activation in the right ventricular outflow tract (RVOT, 90.9ms to 97.7ms, p=0.020). In nine (75%) patients, the area of late activation (defined as >80ms after initial activation) in the RVOT also increased with hydroquinidine. Repolarisation parameters were also affected by hydroquinidine with an increase in QT interval corrected for heart rate (369.5msec vs 434.8msec, p<0.0001) and T-wave width (232.8msec to 271.2msec p=0.003) and a significant reduction in T-wave amplitude (0.4mV to 0.2mV p=0.001) on treatment. The reduction in T-wave amplitude precluded computation of repolarisation time in the RVOT by ECGi on treatment. No difference in the burden of type 1 BrS ECG pattern over 24 hours was seen on 12-lead Holter monitor between baseline and on treatment assessment. No significant difference in serum hydroquinidine level was detected between those who experienced side effects and those who did not (2.9µmol vs 3.1µmol, p=0.790).

Conclusion: Hydroquinidine affects both ventricular activation and repolarisation in patients with BrS and these effects can be detected non-invasively. Further work is required to determine clinical significance of these observed effects and investigate the feasibility of non-invasive monitoring strategy of pharmacotherapy in BrS.