Dronedarone Enhances Rat Aortic and Glomerular Endothelial Nitric Oxide Release in a Dose-Dependent Manner

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Background: Dronedarone is a non-iodinated benzofuran antiarrhythmic agent approved for the treatment of atrial fibrillation. Clinical findings (ATHENA trial) suggest a cardiovascular protective effect beyond rhythm control for dronedarone in patients with elevated risk; however, the underlying mechanism is not understood. As endothelial cell (EC) dysfunction is causally related to atherothrombotic disease, we hypothesized that dronedarone may reduce risk through enhanced nitric oxide (NO) bioavailability.

Methods: WKY rats were treated with dronedarone over a range of doses (5, 10, 20, 30 and 60 mg/kg/day), versus vehicle alone, for 4 weeks. NO and peroxynitrite (ONOO-) release from aortic and glomerular ECs was measured ex vivo using amperometric approaches with nanosensor technology. Maximum release of NO and ONOO- from ECs was stimulated with calcium ionophore (1.0 μM).

Results: In aortic ECs, dronedarone increased NO release by 18% (422 ± 41 to 498 ± 52 nM, p<0.01) at the lowest dose tested and by 90% (422 ± 41 to 800 ± 53 nM, p<0.001) at the highest dose. In glomerular ECs, dronedarone increased NO release by 60% (191 ± 23 to 305 ± 20 nM, p<0.001) at the highest dose tested, with benefits observed at doses as low as 10 mg/kg/day. The ratio of NO to ONOO- release increased significantly in aortic ECs at all dronedarone treatment levels, with an increase of 53% (p<0.001) at 60 mg/kg/day.

Conclusion: Dronedarone enhanced rat endothelial function and NO release in a dose-dependent fashion, especially in aortic tissue. This study provides evidence for a direct vascular benefit with this novel antiarrhythmic agent.