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參展科別 醫學與健康科

作品名稱 **An investigation of the inhibitory potential of Dronedarone on CYP2J2 mediated astemizole metabolism**

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Abstract

Dronedarone is an anti-arrhythmic drug approved in 2009 for paroxysmal and persistent atrial fibrillation. It is less toxic than its predecessor Amiodarone as it does not cause systemic toxicity but has the same pharmacological activity. However the administration of dronedarone to permanent AF and heart failure patients leads to increased risk of stroke and cardiac death. The exact mechanism of the toxicity is currently unknown. Extrahepatic Cytochrome P450 enzymes play a dominant role in organ-specific drug metabolism and toxicity. Cytochrome P450 2J2 (CYP2J2) enzyme, a predominant enzyme found in human cardiac myocytes, metabolizes endogenous arachidonic acid (AA) into epoxyeicosatrienoic acids (EETs) which play an important role in maintaining normal cardiac physiology. Inhibition of CYP2J2 and perturbation of AA metabolic pathway could result in exacerbation of cardiac failure. This research aims to find out whether dronedarone inhibits CYP2J2 in a suitable cell model (H9C2) using astemizole as a probe substrate. Our *in-house* studies using recombinant CYP2J2 enzyme have shown that dronedarone potently inhibits CYP2J2.

Rat myoblast cells (H9C2) will be seeded in 12-well plate and differentiated for 4 days. The cells will be then treated with different concentrations of astemizole and incubated for 24 h. The cells will then be harvested, lysed, and the cell lysate will be analyzed using liquid chromatography-mass spectrometry (LCMS). Using multi-reaction monitoring (MRM) on the LCMS, astemizole concentration as well as its CYP2J2-specific metabolite O-desmethylastemizole concentrations will be measured. The presence of O-desmethylastemizole confirms the metabolism of astemizole by CYP2J2 in H9C2 cells. By plotting a Michaelis-Menten kinetics curve, we will be able to determine the Michaelis constant (K_M) and maximum rate of reaction (V_{max}).

H9C2 cells will be then treated with fixed concentration of astemizole while varying the dronedarone concentration. A decrease in metabolite O-desmethylastemizole conce ntration, indicates inhibition of CYP2J2 metabolism by dronedarone. Using this data, Lineweaver-Burke graph will be plotted, to determine the mode and potency of the inhibition. Our preliminary studies showed that the KM value was 2.7 μ M. This study will be useful in understanding if dronedarone inhibits CYP2J2 which may lead to clinically significant drug-drug interactions, one of the dangers of polypharmacy. Finally this study will shed a new light on the mechanisms for dronedarone mediated cardiac failure exacerbation.

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The aim of the research is to find out whether dronedarone inhibits CYO2JZ in a cell line model. However, the mechanism of why Amiodarone more effective than Dronedarone is not studied.