Concomitant use of ivabradine and cyp3a4 inhibitors in critical cardiac patients

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Background: In recent years there have been warnings concerning drug-induced life-threatening arrhythmias. Drug interactions can increase the risk of QT interval prolongation via interaction of pharmacokinetic mechanism. Some drugs such as Ivabradine does not affect the repolarization or affect the QT interval themselves. However, it can increase the risk of QT prolongation when taken with drugs that block the metabolic breakdown which inhibit the CYP3A4 enzyme particularly. Predisposing factors of QT prolongation include female sex, age over 65 years, brady-arrhythmia, electrolyte disturbances (hypokalemia, hypomagnesaemia), cardiac disease (congestive heart failure, ventricular hypertrophy, myocardial infarction, atrial fibrillation), impaired hepatic/renal function and hypothyroidism.

Purpose: To assess potential Ivabradine – CYP3A4 inhibitor interactions in a Cardiac Critical Care Unit (CCCU).

Method: We prospectively observed patients admitted at CCCU received Ivabradine and CYP3A4 inhibitor (QT prolonging agent) concomitantly from Feb 2018 to July 2018 at National Heart Institute, Malaysia. We use a clinical drug decision support system (CDDSS) to identify the potential drug-drug interactions (PDDI) and assessed the likelihood of drug-drug interactions (DDI) using Drug Interaction Probability Scale (DIPS).

Results: Patients admitted at CCCU co-administered with Ivabradine and CYP3A4 inhibitors (amiodarone/azithromycin) were analyzed. The severity level for both potential Ivabradine – Azithromycin and Ivabradine – Amiodarone interactions were alerted by the CDDSS as Major. Total 10 (M = 70%) patients were screened. The mean age was ± 57 years old. They had no previous exposure to both or one of the medications before. All patients had underlying cardiac disease. The left ventricular ejection fractions (LVEF) ranged from 15% - 65%. Adverse drug event (ADE) occurred in 7 (70%) patients [Male = 5 (71%), Female = 2 (67%)]. 70% of patients had prolonged QT interval induced by Ivabradine – Amiodarone and Ivabradine – Azithromycin. All patients had QTc interval < 500 ms before co-administration and had a change of ± 100 ms after coadministration. The onset of ADE ranged from day 2 to day 5 in all patients. One had life threatening arrhythmia; ventricular fibrillation and require defibrillator and another one patient had non-sustained ventricular tachycardia. The most common precipitating factor was underlying cardiac disease. All suspected precipitating drug was discontinued. DIPS revealed; 57% patients scored 9 points (highly probable DDI) and the rest scored between 5-7 points (probable DDI).

Conclusion: Ivabradine potentially associated to fatal arrhythmia when it is co-administered with CYP3A4 inhibitor. Hence, the physician should reconsider such combination within the correct clinical context to avoid cardiovascular deterioration especially in a critical care setting.