Slow Junctional Rhythm, QTc Prolongation and Transient Torsades de-Pointes following Combined use of Ivabradine, Diltiazem and Ranolazine

SR Mittal *

Abstract
A case of unstable angina developed slow junctional rhythm with QTc prolongation and transient Torsades de pointes following simultaneous use of Ivabradine, Diltiazem and Ranolazine. Effect of Diltiazem on hepatic isoenzyme CYP 3A could be responsible. Such a combination should be avoided.

Case Report

Patients with unstable angina not going for coronary revascularisation need a combination of several antianginals for symptomatic relief. Some of these combinations may have deleterious effect in an individual patient.

One 80 years female presented with unstable angina. Pulse rate was 64/min and blood pressure was 170/100 mmHg. Electrocardiogram revealed T wave inversion in lead I, aVL and V2 to V6. P-R interval was 0.12 seconds and QTc interval was 0.40 sec. (Figure 1). Echocardiography revealed hypertrophy of left ventricular lateral wall and grade 1 diastolic dysfunction. CPK MB was 6 units and Troponin I was negative.

Patient and attendants did not agree for coronary angiography. She was given tab Nicorandil (5 mg x 12 hrly), tab Ivabradine (5 mg x 12 hrly), tab Clopidogrel (300 mg OD), tab Aspirin (350 mg OD), tab Frusemide (20 mg)+Spironolactone (50 mg) (½ BD), tab Diltiazem sustained release (90 mg x 12 hrly) and Inj. Fondaparinux (2.5 mg subcutaneous once daily). After 24 hours, patient felt only mild relief. Pulse rate was 56/min. and blood pressure was 130/86 mmHg. Ranolazine (500 mg x 12 hrly) was added. On third day patient had no episode of angina but pulse rate dropped to 40/min. Electrocardiogram (Figure 2) showed absence of P wave with slow junctional rhythm (37/min) and prolonged QTc (0.47sec) and transient Torsades de pointes.

Fig. 1 : Electrocardiogram showing T wave inversion in Leads I, aVL and V2-V6 with normal QTc interval
Serum electrolytes were normal (Na-123 m.mol/L, K-3.8 m.mol/L, Ca- 10.9 mg/dL, Mg-3.0mg/dL). Ivabradine and Diltiazem were discontinued. Heart rate and QTc interval gradually normalized after three days (Figure 3).

Discussion

Ivabradine selectively inhibits rate of sinoatrial node by selective inhibition of I f current. Diltiazem is a non-dihydropyridine calcium channel blocker with heart rate lowering effect. Combined use of these drugs is expected to have synergistic effect on heart rate. Diltiazem can also inhibit metabolism of Ivabradine by its inhibitory effect on hepatic isoenzyme CYP 3A. Ivabradine and its active metabolite are metabolized by this hepatic isoenzyme. These drugs are, however, not known to cause QT prolongation. Package insert of Ivabradine (Ivabrad), however, suggests avoiding its use in patients with congenital QT syndrome or patients receiving QT prolonging drugs due to QT prolonging effect of bradycardia.

Ranolazine is an inhibitor of the slow inward sodium current. It is known to produce QT prolongation. It is also metabolised by the hepatic isoenzyme CYP 3A. Diltiazem and Verapamil inhibit this isoenzyme and may increase Ranolazine blood levels and hence further increase risk of QT prolongation. Concomitant use of Diltiazem, Ivabradine and Ranolazine resulted in slow junctional rhythm with QTc prolongation and ill sustained torsades de pointes in our patient. Such a combination should be avoided.

References

3. Package insert- Ivabradine tablets (Ivabrad). Lupin LTD
4. Woosly RL. Drugs that prolong the QT interval and/ or induce Torsades de pointes. www.torsades.org. revised 14/07/11