Clopidogrel is Associated With Weaker Platelet Inhibition, Lower Active Metabolite Concentration, and More Poor Responders in Higher Body Weight Patients Compared With Lower Body Weight Patients

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Introduction

In previous studies, patients with body mass index (BMI) ≥25 undergoing PCI had increased platelet reactivity and suboptimal platelet inhibition in response to a 30 µg/mL or 600 mg loading dose (LD) of clopidogrel.

In multivariate analyses of clopidogrel treatment, BMI was the only independent baseline characteristic to predict increased platelet reactivity.2

In comparison to patients in whom platelet inhibition with clopidogrel was suboptimal, patients who demonstrated effective inhibition had a significantly lower BMI.2

In the FEATHER trial,4 a 5 mg maintenance dose (MD) of prasugrel in patients weighing >60 kg (low body weight, LBW) provided platelet inhibition that was non-inferior to that achieved with a prasugrel 10 mg MD in patients weighing 260 kg (higher body weight, HBW) who had stable coronary artery disease (CAD) and were taking aspirin. The platelet inhibitory effect of clopidogrel 75 mg MD was also assessed in LBW and HBW patients.

This analysis compared platelet inhibition, active metabolite concentration, and the percentage of patients showing high on-treatment platelet reactivity (HPR) in LBW and HBW patients taking 75 mg clopidogrel.

Trial Design

This is an analysis of a subset of data from the FEATHER trial, an international, randomized, active comparator, Phase 3b, cross-over study conducted between March 2010 and August 2011.4 After an aspirin run-in period, LBW and HBW patients with stable coronary artery disease were randomly allocated to receive clopidogrel (75 mg/day) and prasugrel (5 mg/day or 10 mg/day) in a double-blind manner. Treatment periods were 12±2 days in duration.

Methods

Pharmacodynamic Analysis

• Light transmission aggregometry (LTA) for maximum platelet aggregation (MPA) in response to 20 µM of adenosine diphosphate (ADP), residual platelet activity (RPA) to 5 µM of ADP, and inhibition of platelet aggregation (IPA) in response to 20 µM of ADP
• VerifyNow P2Y12 (VN2P2Y12) assay used to measure P2Y12 Reaction Units (PRU), and device reported percent inhibition
• Vasodilator-associated stimulated phosphoprotein (VASP) phosphorylation platelet reactivity index (PRI) calculated using flow cytometry

Pharmacokinetic Analysis

• The primary PK parameter was the area under the concentration–time curve calculated through the last quantifiable concentration up to 4 hours post dose, AUC(0-4h)

High On-treatment Platelet Reactivity

• High on treatment platelet reactivity clopidogrel MD was evaluated using the following criteria: MPA to 20 µM ADP <50%, RPA to 20 µM ADP <20%, RPA to 5 µM ADP >14%, VASP-PRI ≤50%, VerifyNow™ P2Y12 PRI >235%, VerifyNow™ P2Y12 inhibition <15%

Results

Baseline characteristics: A two-sample t-test for continuous and Pearson's Chi-square test for categorical variables was used.

In multivariate analyses of clopidogrel treatment, BMI was the only independent variable to predict increased platelet reactivity and suboptimal platelet inhibition in response to a 30 µg/mL or 600 mg loading dose (LD) of clopidogrel.

Mean comparisons for pharmacodynamic (PD) parameters between weight cohorts were conducted using an ANCOVA model with adjustment for site and baseline measurement. The Log-transformed AUC(IPA) was compared between weight cohorts using an ANOVA model with the weight cohort in the model.

The rate of HPR was compared using Fisher's exact test.

In comparison to patients in whom platelet inhibition with clopidogrel was suboptimal, patients who demonstrated effective inhibition had a significantly lower BMI.

The FEATHER study is unique in focusing on a population of LBW and HBW patients with stable CAD who were randomly and blindly assigned to treatment with clopidogrel.

Compared with LBW patients, those with HBW on clopidogrel had:
- lower active metabolite concentration,
- reduced platelet inhibition, and
- a greater incidence of HPR.

These findings may help explain the sub-optimal response to clopidogrel previously reported in patients with higher BMI.

Conclusions


References

Figure 1. Exposure to the active metabolite of clopidogrel in LBW and HBW patients

Figure 2. VASP-PRI versus body weight

Figure 3. Exposure to the active metabolite of clopidogrel versus body weight

Figure 4. VASP-PRI versus body weight

Figure 5. Percent of High On-treatment Platelet Reactivity by Previously Described Criteria

Figure 6. Pharmacodynamic measurements for LBW and HBW patients treated with clopidogrel 75 mg/day for 12±2 Days. Whiskers represent the 10th and 90th percentiles, solid central line is median and dashed line across figures shows the threshold for high platelet reactivity

Figure 7. Pharmacodynamic measurements for LBW and HBW patients treated with clopidogrel 75 mg/day for 12±2 Days. Whiskers represent the 10th and 90th percentiles, solid central line is median and dashed line across figures shows the threshold for high platelet reactivity

Declaration of Interest

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