Abstract: P258

Pharmacometabolomics analysis of plasma and urine to identify clopidogrel exposure metabolic biomarkers

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Introduction: Clopidogrel is a widely used P2Y12 antiplatelet drug. Patient's compliance to clopidogrel is crucial to achieve therapeutic outcome and prevent thromboembolic events. While measuring serum level of clopidogrel and/or its active metabolite may indicate compliance, many confounding factors interfere, however, often compromising the reliability of the results. Identifying drug exposure metabolic biomarkers is reliable and fast tool to evaluate patient's compliance, as well as getting in-depth information on the metabolic perturbation associated with drug exposure. We hypothesized that Nuclear magnetic resonance (1HNMR) pharmacometabolomics analysis of plasma and urine can phenotype clopidogrel loading dose (LD) in coronary artery disease (CAD) patients.

Purpose: We aimed to phenotype clopidogrel exposure in plasma and urine of CAD patients using 1HNMR pharmacometabolomics.

Methods: We analysed pre-dose and post-dose plasma and urine samples from 79 CAD patients who had clopidogrel 600 mg LD using 1HNMR pharmacometabolomics technique. Data analysis of 1HNMR spectra was performed by developing preliminary orthogonal partial least square discriminant analysis models (OPLS-DA). This was followed by univariate logistic regression (ULR), factor analysis (FA) and multivariate logistic regression (MVLR) for the 1HNMR spectral regions with variable influence on projection (VIP) > 1 in the OPLS-DA preliminary models to indicate the best discriminating models (metabotypes). Area under receiver operating characteristic (AUROC) was used to evaluate the OPLS-DA and MVLR models.

Results: OPLS-DA models discriminated between pre-dose and post-dose in plasma and urine with accuracy of 91.77% and 100%, respectively. MVLR indicated final plasma and urine metabotypes with accuracy of 84.2% and 82.2%, respectively. From the final exposure metabotypes, 27 and 20 metabolites were found perturbed in plasma and urine upon exposure to clopidogrel LD, respectively.

Conclusion: 1HNMR pharmacometabolomics analysis of plasma and urine was efficient in phenotyping clopidogrel exposure with good accuracy. The study is ongoing to indicate metabolic pathways associated with clopidogrel exposure.

<table>
<thead>
<tr>
<th>Metabotype</th>
<th>OPLS-DA Model</th>
<th>MVLR Model</th>
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<tbody>
<tr>
<td></td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Plasma</td>
<td>96.20%</td>
<td>87.34%</td>
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<tr>
<td>Urine</td>
<td>100%</td>
<td>100%</td>
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OPLS-DA: orthogonal partial least square discriminant analysis, MVLR: multivariate logistic regression, AUROC: Area under receiver operating characteristic