Prediction of the effect of renal impairment on the pharmacokinetics of new drugs

Clinical Pharmacokinetics

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Table 2 PK characteristics for the five drugs used as test dataset.

<table>
<thead>
<tr>
<th>Generic</th>
<th>CL/F (L/h)</th>
<th>F (%)</th>
<th>CL (L/h)</th>
<th>Ae (%)</th>
<th>ppb (%)</th>
<th>E_H (-)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>90</td>
<td>10</td>
<td>36</td>
<td>93.5</td>
<td>9.09</td>
<td>[1]</td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>11.94</td>
<td>95</td>
<td>11.34</td>
<td>84</td>
<td>40</td>
<td>10.19</td>
<td>[2]</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
<td>164.4</td>
<td>6.5</td>
<td>106.86</td>
<td>80</td>
<td>35</td>
<td>51.66</td>
<td>[3]</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>42</td>
<td>77.75</td>
<td>7.32</td>
<td>60</td>
<td>43.74</td>
<td>[4]</td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td>517</td>
<td>83.8</td>
<td>0</td>
<td>90</td>
<td>45.59</td>
<td>[5]</td>
<td></td>
</tr>
</tbody>
</table>

Ae fraction of dose excreted unchanged in urine, CL intravenous plasma clearance, CL/F oral clearance, E_H hepatic extraction ratio, F absolute bioavailability, ppb plasma protein binding. References in the table are reported below:

Fig. 1 Univariate single regression. In the first row AUC ratio predictions vs Ae plots with regression line, in the second row experimental values vs predictions plots with identity line, in the third row fold change vs predictions plots. Mild, moderate and severe renal impairment results are reported in the first, second and third column, respectively.
**Fig. 2** Univariate single regression. In the first row AUC ratio predictions vs ppb plots with regression line, in the second row experimental values vs predictions plots with identity line, in the third row fold change vs predictions plots. Mild, moderate and severe renal impairment results are reported in the first, second and third column, respectively.
**Fig. 3** Univariate single regression. In the first row AUC ratio predictions vs $F \cdot Ae/(1-\text{ppb})$ plots with regression line, in the second row experimental values vs predictions plots with identity line, in the third row fold change vs predictions plots. Mild, moderate and severe renal impairment results are reported in the first, second and third column, respectively.
Fig. 4 Univariate multiple regression with regressors Ae and ppb for the severe level of renal impairment. Experimental values vs predictions plot with identity line on the left, fold change vs predictions plot on the right.
Fig. 5 Outcome of the PLS-NIPALS regression: circle of correlations.
Fig. 6 Outcome of the PLS-NIPALS regression: coefficients of PLS-regression.
Fig. 7 PLS-NIPALS regression. Experimental values vs predictions plot on the first row, fold change vs predictions plot on the second row for mild, moderate and severe level of renal impairment in the first, second and third column, respectively.
Fig. 8 Univariate single regression (with regressor Ae) for mild level of renal impairment (validation dataset). Experimental values vs predictions plot on the left, fold change vs predictions plot on the right. Predictions and fold changes obtained with the validation dataset are reported with filled circles.
Fig. 9 Univariate single regression (with regressor Ae) for moderate level of renal impairment (validation dataset). Experimental values vs predictions plot on the left, fold change vs predictions plot on the right. Predictions and fold changes obtained with the validation dataset are reported with filled circles.
Fig. 10 Univariate multiple regression (with regressors Ae and ppb) for severe level of renal impairment (validation dataset). Experimental values vs predictions plot on the left, fold change vs predictions plot on the right. Predictions and fold changes obtained with the validation dataset are reported with filled circles.