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Background

• Free phenytoin (PHT) concentration reflects efficacy and toxicity
• Low albumin concentration may affect total PHT concentration and free fraction, but usually causes no change in free concentration
• Cannot estimate free PHT concentration from total PHT concentration when free fraction is unknown
• Winter-Tozer equation most commonly used to predict free PHT concentration
• Overall predictive performance of this equation is poor
• Other studies found bias and imprecision and developed their own equations, which have not been validated in other studies

Methods

• Retrospective chart review at Vancouver General Hospital from Sept 2008 to Sept 2013
• Inclusion: > 18 years old, free PHT level
• Exclusion: level is not at steady state; patients on carbamazepine, phenobarbital, valproic acid, and hemodialysis
• Convenience sample size of ~50 patients per subgroup (Critical Care, General Medicine, Neurology)
• Mean predictive error (MPE) to assess bias and root mean square error (RMSE) to assess precision

Primary objective:

• To assess the bias and precision of the Winter-Tozer equation and its derivatives in predicting free PHT concentrations in different patient subpopulations

Secondary objective:

• To assess the effect of age, gender, eGFR, and total daily dose on the bias and precision of the Winter-Tozer equation and its derivatives
• To derive new equations that will better predict free PHT concentration

Exclusion Flow Chart

Table 1: Summary of Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 123)</th>
<th>Critical Care (n = 36)</th>
<th>General Medicine (n = 50)</th>
<th>Neurology (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.9 (18.0)</td>
<td>57.0 (17.9)</td>
<td>74.0 (14.0)</td>
<td>56.0 (20.0)</td>
</tr>
<tr>
<td>Gender, Male</td>
<td>71 (53%)</td>
<td>26 (72%)</td>
<td>24 (49%)</td>
<td>21 (51%)</td>
</tr>
<tr>
<td>Scr (µmol/L)</td>
<td>90.4 (64.0)</td>
<td>104 (74.8)</td>
<td>96.8 (75.0)</td>
<td>70.3 (16.3)</td>
</tr>
</tbody>
</table>

Equation 1: Winter-Tozer

Predicted Free PHT = Measured Total PHT × 0.25 × Albumin × 0.1

Equation 2: Kane et al.

Predicted Free PHT = Measured Total PHT × 1.8 × (0.5 × 4) × 0.1 × 0.25 × Albumin × 0.1

Equation 3: Kane et al.

Predicted Free PHT = 0.40376 × Measured Total PHT + 0.78075

Equation 4: Equation Derived from All Patients

Predicted Free PHT = Measured Total PHT × 0.25 × Albumin × 0.1

MPE = \frac{1}{n} \sum \text{Predicted Free PHT} - \text{Measured Free PHT}

RMSE = \sqrt{\frac{1}{n} \sum \text{Predicted Free PHT} - \text{Measured Free PHT}^2}

Equation 1 (Winter-Tozer)\(^1\)

Predicted Free PHT = Measured Total PHT × 0.25 × Albumin × 0.1

Table 2: Bias and Precision Per Subgroup

<table>
<thead>
<tr>
<th>Equation</th>
<th>All (n = 123)</th>
<th>Critical Care (n = 36)</th>
<th>General Medicine (n = 50)</th>
<th>Neurology (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPE (µmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.7 (1.5 to 1.9)</td>
<td>1.4 (0.7 to 2.1)</td>
<td>1.7 (1.4 to 2.0)</td>
<td>1.6 (0.5 to 2.2)</td>
<td></td>
</tr>
<tr>
<td>-0.2 (-0.4 to 0.4)</td>
<td>-0.3 (-0.6 to 0.2)</td>
<td>-0.1 (-0.3 to 0.1)</td>
<td>0.2 (0.0 to 0.4)</td>
<td></td>
</tr>
<tr>
<td>3.0 (-0.6 to 1.8)</td>
<td>-1.1 (-1.7 to -0.5)</td>
<td>5.0 (4.7 to 5.3)</td>
<td>0.2 (0.0 to 0.4)</td>
<td></td>
</tr>
<tr>
<td>0.8 (0.5 to 0.9)</td>
<td>0.0 (0.7 to 0.7)</td>
<td>0.5 (0.3 to 0.7)</td>
<td>0.9 (0.7 to 1.1)</td>
<td></td>
</tr>
<tr>
<td>Precision (RMSE) (µmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2 (1.2 to 3.2)</td>
<td>2.5 (0.3 to 4.8)</td>
<td>2.1 (0.4 to 3.8)</td>
<td>2.2 (0.3 to 3.5)</td>
<td></td>
</tr>
<tr>
<td>1.4 (0.2 to 2.6)</td>
<td>2.3 (1.6 to 4.4)</td>
<td>0.9 (0.3 to 1.5)</td>
<td>0.7 (0.5 to 0.9)</td>
<td></td>
</tr>
<tr>
<td>1.3 (0.5 to 2.1)</td>
<td>2.0 (0.4 to 4.4)</td>
<td>1.1 (0.4 to 1.8)</td>
<td>0.8 (0.6 to 1.5)</td>
<td></td>
</tr>
<tr>
<td>1.4 (0.0 to 2.2)</td>
<td>2.0 (0.8 to 4.8)</td>
<td>1.5 (0.4 to 1.6)</td>
<td>1.1 (0.7 to 1.5)</td>
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Table 3: Bias and Precision for Age, Gender, and eGFR

Table 4: Bias and Precision of New Equations

Table 5: Dose Changes Made From Predictive Equations

Results

• The Winter-Tozer equation tended to overpredict
• The Kane et al. equations (Equation 2 and 3) tended to underpredict
• The Anderson et al. equation generally overpredicted
• In general, there was more bias and imprecision associated with the Winter-Tozer equation than the other equations

Conclusion

• The overall predictive performance of the Winter-Tozer equation in this population was poor
• We developed new derivative equations with reduced bias