The pharmacokinetics and –dynamics of propofol during awake craniotomy

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Background
During an awake craniotomy, the patient is under general anesthesia during the beginning and the end of surgery. However, he needs to be fully awake and cooperative during surgery in order to undergo neurological testing.

This calls for a precise management of anesthesia which in turn requires accurate pharmacokinetic-dynamic models of propofol.

Aim of the study
Comparison of the pharmacokinetic-dynamic models

• of Marsh et al. (pk/pd Marsh, [1]) and

• of Schnider et al. (pk/pd Schnider, [2]) regarding the following questions:

Which pk/pd model predicts
• propofol plasma concentrations and
• depth of anesthesia more precisely?

Methods
Prospective observational trial

• n=13 patients suffering from epileptic foci or brain tumors in close proximity to the speech centre

• Awake craniotomy using the asleep-awake-asleep-technique

• Continuous monitoring of
• propofol infusion rates
• depth of anesthesia, monitored as BIS value; BIS-Vista Monitor, Covidien

• Regular sampling of arterial blood to measure propofol plasma concentration using HPLC

Pharmacokinetic calculations
• Calculation of propofol plasma concentrations (Cpl) according to pk/pd Marsh and pk/pd Schnider

• Calculation of the prediction error PE

\[ \text{PE} = \left( \frac{C_{\text{measured}} - C_{\text{calculated}}} {C_{\text{calculated}}} \right) \times 100\% \]

• Calculation of the median prediction error (MDPE) and the median absolute prediction error (MDAPE)

Pharmacodynamic Calculations
• Calculation of the effect-site concentration (C_e) of propofol using the elimination constant k_e:

\[ \text{dC}_e / \text{dt} = (\text{C}_{\text{pl}} - \text{C}_e) \times k_e \]

• Three methods to determine ke:

  1. original: using the published values for k_e

  2. fit: using individually fitted values for k_e

  3. t_peak: using a k_e which results in a “time-to-peak” of 1.6 minutes

• Evaluation of the sigmoid relation between C_e and the effect E (= 100 – BIS)

\[ E = E_0 + \left( E_{\text{max}} - E_0 \right) \times \frac{C_e^{\lambda}}{(C_{50}^{\lambda})^\lambda + C_e^{\lambda}} \]

\[ E_{\text{max}} = \text{maximum effect with propofol} \]

\[ E_0 = \text{effect without propofol} \]

\[ C_{50} = C_e \text{, which results in 50% of } E_{\text{max}} \]

\[ \lambda = \text{steepness of the curve} \]

• Calculation of the prediction probability P_E [3], by which C_e can be predicted based on the BIS

Data = mean ± standard deviation

Results

Plasmaconcentrations of propofol

Figure 1: Comparison between the propofol plasma concentrations calculated according to pk/pd Marsh and pk/pd Schnider as well as pk/pd Marsh and the measured plasma concentrations in our patients’ arterial blood samples

<table>
<thead>
<tr>
<th>Patient</th>
<th>Marsh</th>
<th>Marsh</th>
<th>Marsh</th>
<th>Marsh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>0.260</td>
<td>0.40 ± 0.14</td>
<td>0.456</td>
<td>0.15 ± 0.04</td>
</tr>
<tr>
<td>Fit</td>
<td>0.38 ± 0.05</td>
<td>0.79 ± 0.06</td>
<td>0.81 ± 0.06</td>
<td>0.79 ± 0.05</td>
</tr>
</tbody>
</table>

Figure 2: Median prediction error MDPE and median absolute prediction error MDAPE for the plasma concentrations of propofol calculated according to pk/pd Marsh and pk/pd Schnider

Table 1

<table>
<thead>
<tr>
<th>Pharmacokinetic model</th>
<th>Median prediction error MDPE</th>
<th>Median absolute prediction error MDAPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsh</td>
<td>-12 ± 14 %</td>
<td>0.4 ± 0.2 %</td>
</tr>
<tr>
<td>Schnider</td>
<td>16 ± 20 %</td>
<td>0.8 ± 0.3 %</td>
</tr>
</tbody>
</table>

Conclusion

• In this study, the model according to Schnider et al. achieved the most precise results. We therefore recommend this model for awake craniotomies.

• There are significant interindividual differences in prediction probabilities and pharmacodynamic parameters, hence we suggest to monitor depth of anesthesia during awake craniotomy.

Literature