The scopolamine challenge model remains an important assay of CNS penetration and target engagement for drug developers. Delayed PD effect has implications for timing of dosing and assessments given the potential for hysteresis with either or both scopolamine and the reversal agent.

**Results**

**Scopolamine PK**

- \( C_{\text{max}} \) for scopolamine was 1.69 ng/mL, with \( T_{\text{max}} \) around 0.5 hours post-dose and T1/2 around 1.5 hours (see Figure 1).
- This was largely unchanged in the presence of donepezil.

**Donepezil PK**

- \( C_{\text{max}} \) for donepezil was 18.53 ng/mL, with \( T_{\text{max}} \) around 3 hours post-dose, but T1/2 beyond sampling duration.
- Washout for donepezil was incomplete with pre-dose concentrations in periods following donepezil between 0.49 and 4.7% of \( C_{\text{max}} \).

**Effects of scopolamine on cognition and self-ratings**

- Medium to large effects of scopolamine were evident for all cognitive parameters and self-rated alertness.
- Effects tended to peak at 2 hours post-scopolamine but were also prominent at 1 and 3 hours.

**Donepezil showed partial reversal of scopolamine for executive function at 1 and 2 hours, information processing speed at 1 hour, and working memory at 2 hours (p<0.03).**

**Conclusions**

- Delay in PD effects with scopolamine has been shown previously and the present data extend these findings to additional, relevant domains of cognition including processing speed, visual attention, working memory, visual learning and executive functions.
- Delayed PD effect has implications for timing of dosing given the potential for hysteresis with either or both scopolamine and the reversal agent.
- Given the ability of donepezil to partially reverse cognitive effects of scopolamine in the absence of any effect on self-ratings, there is likely no concern that subjective sedation needs to be considered in the analysis and interpretation.

**Table 1: Demographic Data**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Gender</th>
<th>Race</th>
<th>White/Caucasian</th>
<th>N (% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.7 (5.77)</td>
<td>Race</td>
<td>White/Caucasian</td>
<td>N (%)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177.3 (6.96)</td>
<td>Height (kg)</td>
<td>77.66 (10.38)</td>
<td>BMI (kg/m²)</td>
</tr>
</tbody>
</table>

**Table 2: Cognition and self-rating assessments**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Cognitive domain</th>
<th>Outcome measure</th>
<th>Cognitive domain</th>
<th>( C_{\text{max}} ) of scopolamine in the subject</th>
<th>( T_{\text{max}} ) of scopolamine in the subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction time</td>
<td>Simple reaction time</td>
<td>Reaction time</td>
<td>Visual learning</td>
<td>Speed of performance; mean of the log</td>
<td>Speed of performance; mean of the log</td>
</tr>
<tr>
<td>Stroop</td>
<td>Color-word interference</td>
<td>Stroop</td>
<td>Visual learning</td>
<td>Speed of performance; mean of the log</td>
<td>Speed of performance; mean of the log</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>Number of errors made over five learning trials</td>
<td>Delayed Recall</td>
<td>Visual learning</td>
<td>Speed of performance; mean of the log</td>
<td>Speed of performance; mean of the log</td>
</tr>
<tr>
<td>GMR</td>
<td>Absolute difference between reaction times</td>
<td>GMR</td>
<td>Visual learning</td>
<td>Speed of performance; mean of the log</td>
<td>Speed of performance; mean of the log</td>
</tr>
</tbody>
</table>

**Figure 1: Scopolamine PK and effect size Impaired to executive function (GMR)\( \text{g} \)**


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 methods documented in the design of scopolamine challenge studies for proof of concept trials? In 2018, 11% of AD therapies in clinical development (13 agents) were symptomatic cognitive enhancers, with cholinergic target being a major proportion of these. The scopolamine challenge model is an assay of CNS penetration and target engagement, providing confidence for drug developers before designing clinical trials. However, the model has been relatively infrequently used in recent clinical development. Methodological questions regarding importance of sedation to cognitive impairment, timing of dosing for reversal agents, duration of washouts, timing of pharmacodynamic assessments, and approaches to statistical analysis still need to be addressed.

**Methods**

- This was a double blind, placebo controlled, randomized, three-way incomplete crossover study of 0.5 mg scopolamine hydrobromide, 10 mg donepezil hydrochloride, and matched placebo.
- Cognition, self-rated alertness and mood were assessed pre-donepezil and 1, 2, 3 hours post-scopolamine (4, 5, 6 hours post-donepezil) using a computerized test battery.
- Blood sampling was performed pre, and 3, 4, 5, 6 hours post-donepezil; and pre, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 hours post-scopolamine, for donepezil and scopolamine PK.
- The study consisted of three treatment periods separated by 2 weeks wash-out, and a follow-up phone call.
- Data were listed and described by treatment and time using summary statistics.
- For cognition and self-ratings, effect size (Cohen’s d), was calculated.