Methodological insights from an exploratory pharmacokinetic/ pharmacodynamic study of scopolamine and donepezil in healthy males

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Introduction

- How do PK/PD data inform 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 targets making-up a significant proportion of these
- The scopolamine challenge model is an assay of CNS penetration and target engagement, providing confidence for drug developers before designing PIIb studies
- 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 placebos
- 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, 0.75, 1, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8 hours post-scopolamine, for donepezil and scopolamine PK
- The study consisted of screening, 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

Table 1: Demographic Data

Characteristic	Category	Mean SD	N (%)
			24 (100)
Age (years)		30.7 (6.77)	
	Race		
	White/Caucasian		15 (62.5)
	Caucasian		1 (4.17)
	Black		2 (8.33)
	African		3 (12.50)
	Asian or Pacific Islander		2 (8.33)
	Mixed		1 (4.17)
Height (cm)		177.3 (6.89)	
Weight (kg)		77.68 (10.358)	
BMI (kg/m^2)		24.68 (2.488)	

Table 2: Cognition and self-rating assessments

Test name/ component	Test paradigm	Cognitive domain	Outcome measure	Avg. time required
Groton Maze Learning (GMLT)	Hidden-pathway maze learning	Executive function	Number of errors made over five learning trials (Lower score = better performance)	7 minutes
Groton Maze – Delayed Recall Condition (GMLD)	Hidden-pathway maze learning	Long-term memory	Number of errors made in remembering the maze pathway after a delay (Lower score = better performance)	1 minute
Detection (DET)	Simple reaction time	Psychomotor function	Speed of performance; mean of the $\log_{10}$ transformed reaction times for correct responses (Lower score = better performance)	3 minutes
Identification (IDN)	Choice reaction time	Attention	Speed of performance; mean of the $\log_{10}$ transformed reaction times for correct responses (Lower score = better performance)	3 minutes
Two Back (TWB)	N-back working memory	Working memory	Speed of performance; mean of the $\log_{10}$ transformed reaction times for correct responses (Lower score = better performance)	4 minutes
One Card Learning (OCL)	Pattern separation	Visual learning	Accuracy; Arcsine transformation (Higher score = better performance)	6 minutes
Self-rated Alertness (ALERT)	Bond and Lader Visual Analogue Scales	Alertness	Position on scale in mm (Higher score = greater self-rated alertness)	1 minute
Self-rated Contentedness (CONT)	Bond and Lader Visual Analogue Scales	Contentedness	Position on scale in mm (Higher score = greater self-rated contentment)	1 minute
Self-rated Calmness (CALM)	Bond and Lader Visual Analogue Scales	Calmness	Position on scale in mm (Higher score = greater self-rated calmness)	1 minute

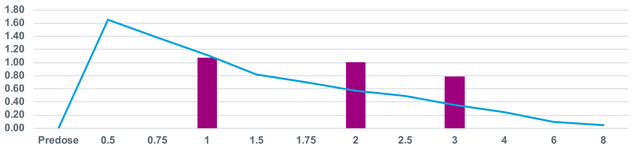
The scopolamine challenge model remains an important assay of CNS penetration and target engagement for drug developers. Delayed PD effect has implications for timing of dosing and assessments given the potential for hysteresis with either or both scopolamine and the reversal agent.

Results

Scopolamine PK

- C_{max} for scopolamine was 1.69 ng/mL, with T_{max} around 0.5 hours post-dose and T½ around 1.5 hours (see Figure 1)
- This was largely unchanged in the presence of donepezil

Figure 1: Scopolamine PK and effect size impairment to executive function (GMLT)

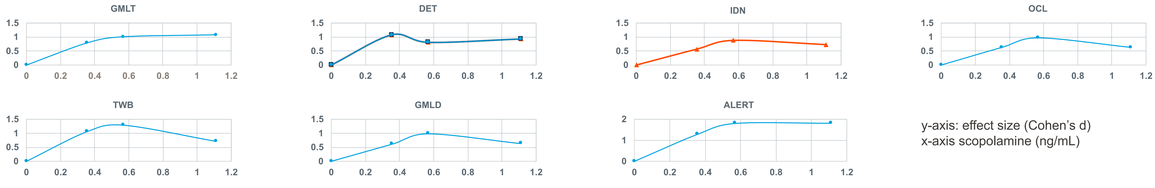


Donepezil PK

- C_{max} for donepezil was 18.53 ng/mL, with T_{max} around 3 hours post-dose, but T½ beyond sampling duration
- Washout for donepezil was incomplete with pre-dose concentrations in periods following donepezil between 0.49 and 4.7% of C_{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



y-axis: effect size (Cohen's d)
x-axis scopolamine (ng/mL)

Donepezil showed partial reversal of scopolamine for executive function at 1 and 2 hours, information processing speed at 1 hours, and working memory at 2 hours (d ≥0.3)

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

One or more authors report potential conflicts which are described in the program. The authors are full time employees of the respective companies (Parexel and Cogstate).
Disclosures:
Matthias Mohse and Tania Hugo are employees of Parexel International. parexel. Paul Maruff, Pawel Kalinowski and Chris J. Edgar are employees of Cogstate. Cogstate