Reversal of Mecamylamine Induced Effects in Healthy Subjects by Nicotine Receptor Agonists: Cognitive and (Electro)Physiological Responses.

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INTRODUCTION

Developing a nicotinic pharmacological challenge model could be an important tool to understand the complex role of the nicotinic cholinergic system in cognition, and to aid in early proof of pharmacology of novel compounds acting on the nicotinic acetylcholine receptor.

AIM

Effects of nicotinic antagonist mecamylamine on a battery of cognitive and neurophysiological tests; effects of nicotine or galantamine co-administration on reversing the cognitive impairments caused by mecamylamine.

METHODS

Randomized, double-blind, double-dummy, placebo-controlled, four way cross-over study of a single oral dose of mecamylamine (30 mg) in combination with either a cholinesterase inhibitor (16 mg galantamine) or a nicotinic agonist (21mg nicotine) and matching placebos.

- **Safety**: adverse events (AEs), clinical laboratory, ECG, vital signs.
- **PK**: model for individual concentration time profiles of mecamylamine.
- **PD**: NeuroCart computerized test battery for repeated assessment of attention, episodic and working memory, executive functioning, pharmaco-EEG, pupillometry and visual analogue scales (VAS) for mood and drug effects, including nausea question.

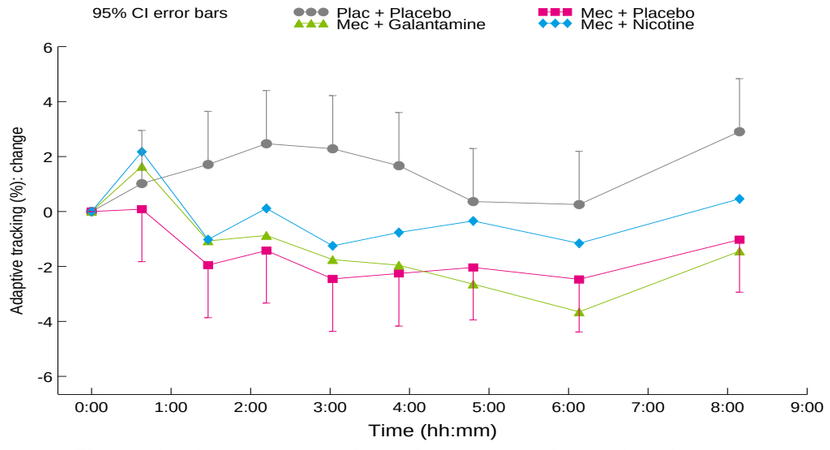

Figure 1: effect on attention, alertness and reaction time

RESULTS

Mecamylamine 30 mg induced significant disturbances of cognitive functions in healthy subjects. Attention and execution of visual/fine motor tasks was decreased, short- and long term memory was impaired and reaction time was increased compared to placebo. Also, posterior α and β power was decreased on the EEG which was reversed by nicotine co-administration. Memory and motor coordination test effects could partially be reversed by co-administration of nicotine.

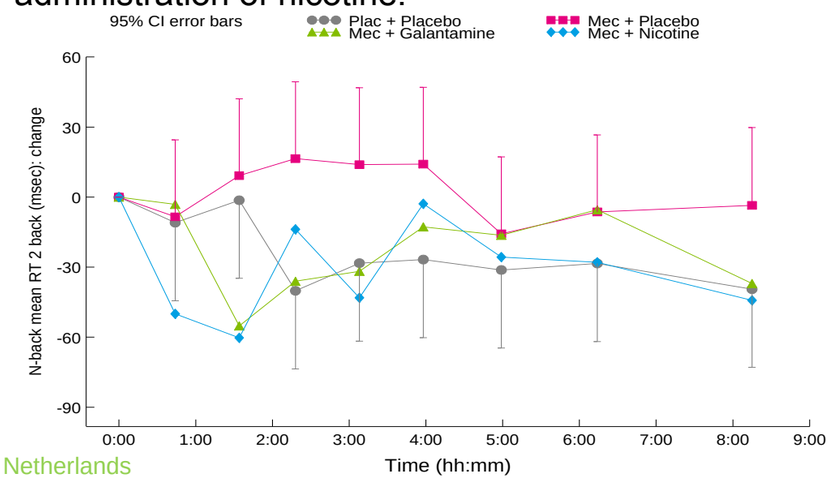

Figure 2: reaction time and short term memory

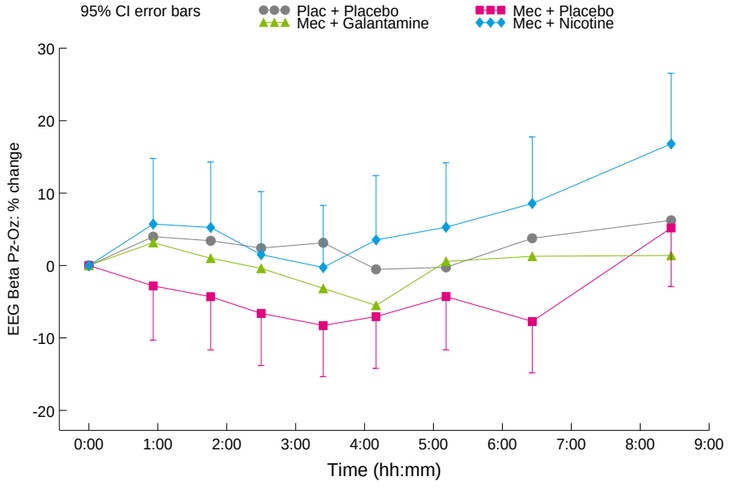

Figure 3: effect on the EEG: Beta frequency over Pz-Oz

CONCLUSIONS

The mecamylamine challenge model can be used for PoP studies targeting nAChR.

Mecamylamine:

- Was safe and generally well tolerated
- Decreased motor coordination
- Decreased attention and executive functioning
- Worse short- and long term memory
- Decreased α and β Pz-Oz activity

→ Effects (partially) reversed by nicotine, to a lesser extent by galantamine.

Results of this study suggest that the mecamylamine challenge model can be used for proof-of-pharmacology studies with nicotinic ACh receptor agonists in healthy subjects, providing a useful tool in drug development of cognition enhancing compounds currently being developed to treat for instance Alzheimer's disease and schizophrenia.

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