Response to an acute pharmacological challenge with galantamine as a predictor for responsiveness to treatment

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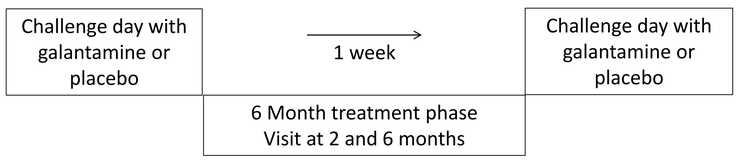
Introduction

Cholinesterase inhibitors are often prescribed to patients with AD. Only approximately a third of patients with AD respond favorably to treatment with a CEI. It is difficult to predict which patient will respond and which will not. This leads to many patients who are unnecessarily treated and exposed to possible adverse drug effects. It is hypothesized that reactivity to an acute cholinergic pharmacological challenge with galantamine may predict clinical responsiveness after a 6-month treatment in patients with AD.

Methods

This is a double-blind, placebo-controlled, randomized crossover study with galantamine in 50 patients with mild to moderate AD (MMSE 18-26), followed by six month treatment with galantamine.

- Challenge phase: galantamine 8 or 16 mg or placebo.
- Treatment phase: galantamine extended release in an escalating dose, starting with 8 mg per day for one month, and increasing to 16 mg per day if there are no side-effects.
- Follow-up visits occur at 2 and 6 months and comprise clinical scales (table 1).



Results

- 50 patients were included in the study.

Challenge phase: 2 patients dropped out,
difference between galantamine and placebo was found on saccadic reaction time (-0.0099, CI -0.0195 - -0.0003, p=0.0430), EEG alpha Fz-Cz (-14.9% change from baseline (CFB), CI -21.0 - -8.3, p=0.0002), EEG beta Fz-Cz (-12.6% CFB, CI -19.4 - -5.3, p=0.0019) and EEG theta Fz-Cz (-17.9% CFB, CI -25.0 - -10.0, p=0.0001).

Treatment phase: 5 patients dropped out, 32 patients were defined as non-responder and 11 patients as responder to galantamine treatment. When comparing challenge results between responders and non-responders to the 6 month treatment, the responders had a significantly higher decrease of EEG alpha Fz-Cz (-20.4%, CI -31.6 - -7.5, p=0.0045), EEG beta Fz-Cz (-15.7%, CI -28.3 - -0.9, p=0.0388) and EEG theta Fz-Cz (-25.9%, CI -38.4 - -10.9, p=0.0024) after acute administration of galantamine.

Conclusions

- 11 out of 43 patients were defined as responder to galantamine treatment.
- A pharmacological challenge with galantamine in patients with mild to moderate AD induces acute, measurable effects on saccadic reaction time and frontal EEG parameters.
- The decrease on frontal alpha, beta and theta EEG activity is significantly more extensive in responders to a six month treatment with galantamine.
- Reduction of unnecessarily treated patients with approximately 60%.

Outcome measures challenge phase (with NeuroCart):
- Memory: facial encoding and recognition task, visual verbal learning test, N-back task
- Attention: adaptive tracking, simple reaction time task, VAS for alertness, mood and calmness
- Pharmaco-EEG, pupil size, eye movements

Outcome measures treatment phase:
- ADAS-COG
- Clinical dementia rating scale – sum of boxes (CDR)
- Disability assessment for dementia (DAD)
- Mini mental state examination (MMSE)
- Neuropsychiatric inventory (NPI)

Table 1

Figure 1: NeuroCart

The NeuroCart is a computerized multimodal test battery that covers all CNS domains and allows for multiple testing in clinical trials.

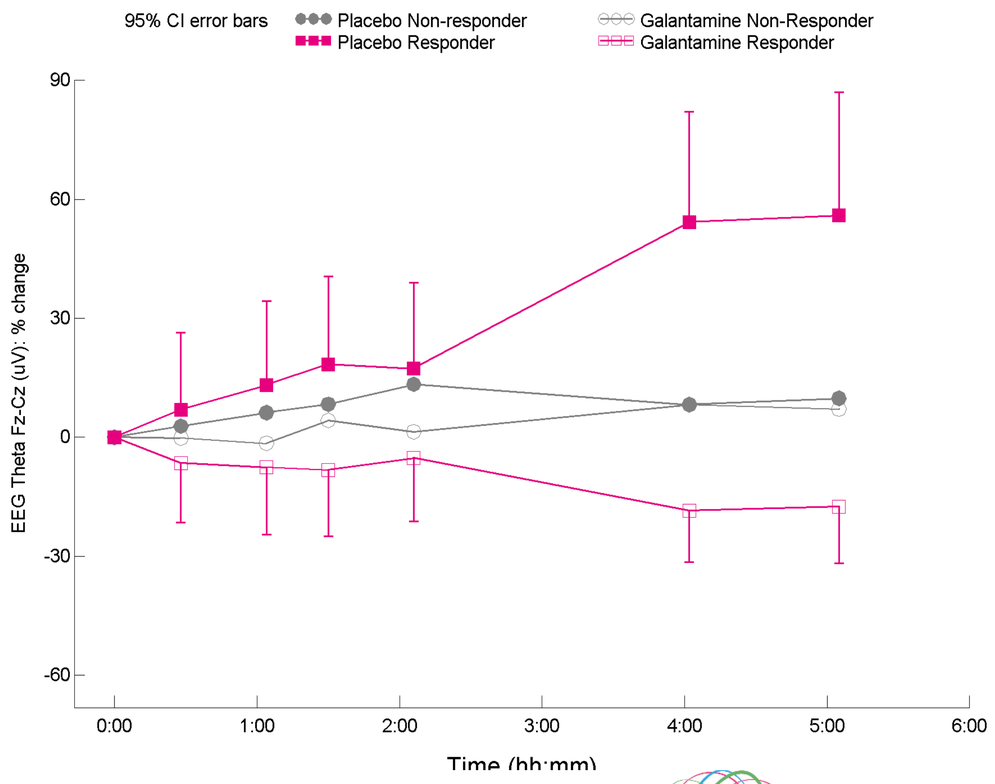


Figure 2: EEG

Theta Fz-Pz % change from baseline

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