REVERSAL OF SCOPOLAMINE-RELATED DEFICITS IN COGNITIVE FUNCTIONS BY ZT-1, A HUPERZINE-A DERIVATIVE

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Introduction

When scopolamine is administered to healthy volunteers, a similar profile of cognitive deficits is produced to that seen in Alzheimer’s disease (AD). This has led to the development of the ‘scopolamine model’ used to evaluate the potential of novel compounds in treating the cognitive deficits associated with AD.

The CDR system has proven sensitivity in the scopolamine model of dementia and compounds developed for the treatment of the dementia.

ZT-1 is a huperzine A derivative, which is known to be a reversible, potent and selective acetylcholinesterase inhibitor.

Methods

The aim of this study was to determine potential actions of ZT-1 in reversing scopolamine-induced cognitive and mood decline in healthy elderly volunteers compared to donepezil.

The study was a 4-way, repeated-measures, cross-over design. On each occasion the volunteers received a subcutaneous injection of scopolamine.

Cognitive tasks (CDR Computerised Assessment System) assessing functions including attention, working memory and episodic secondary memory, were administered pre- and 45 minutes post scopolamine injection, to identify the impairment produced by the compound.

Then, in double-blind fashion, the volunteers were dosed with either placebo, ZT-1 1.0 mg, ZT-1 1.5 mg or donepezil 1.0 mg. The CDR tasks were then re-administered at 0.75 hours, 2 hours, 4.5 hours and 6 hours to determine the extent to which the treatments could reverse the impairments produced by scopolamine.

Results

Scopolamine effect

The tasks all showed a high sensitivity to scopolamine challenge, and on the majority of the measures the initial impairments produced by scopolamine were equivalent. Further, there was a profile of recovery post-scopolamine, on these measures.

Discussion

Overall, ZT-1 was able to reduce the cognitive and mood impairments produced by scopolamine on tasks measuring attention, working memory, episodic secondary memory, eye-hand co-ordination and mood. This was evidenced in superior performance compared to placebo and effects, which were comparable in direction and often magnitude to those of donepezil. There is some indication of a dose-dependent effect with a very encouraging profile of benefits to attention, working memory, recall and recognition under 1.0 mg ZT-1, which in some cases is as good as those seen under donepezil. The 1.5 mg dose may produce similar benefits, though less pronounced on some measures, with a possible additional benefit to attention.

Conclusion

There was a clear indication from the present study that ZT-1 can be effective in reversing scopolamine-induced cognitive impairment compared to placebo and positive control (donepezil). There were also some indication of a better recovery profile than donepezil, in terms of earlier onset, longer duration of action and greater magnitude of recovery. Our data clearly indicate further clinical research with ZT-1 should be undertaken.

References