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

Andrea Zangara[1], Chris Edgar[12] , Keith Wesnes[12], Pietro Scalfaro[3], Hervé Porchet[3]

[1]Human Cognitive Neuroscience Unit, Northumbria University, Newcastle upon Tyne, UK [2]CDR Ltd., Goring-on-Thames, UK , [3]Debiopharm SA., Lausanne, Switzerland

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 dementias.

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

Method

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 10 mg. The CDR tasks were then re-administered at 0.5 hours, 2 hours, 4.5 hours and 6 hours to determine the extent to which the treatments could reverse the impairments produced by scopolamine.

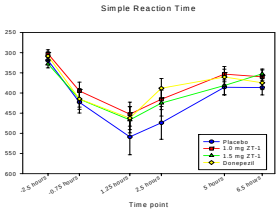
Results

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.

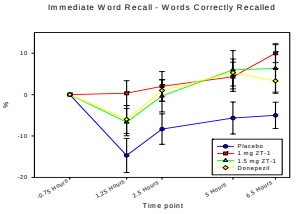
Results

Attention



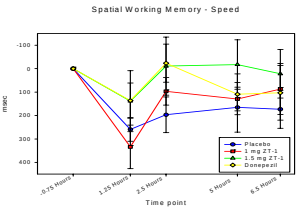
The first two time points of the Simple Reaction Time graph reflect the impairments with scopolamine. The next 4 illustrate the opportunity for the study compounds to prevent further impairment and/or to increase recovery over placebo. The comparisons from the ANOVA showed in this case significant overall benefits for both 1.5 mg ZT-1 ($p=0.02$) and donepezil ($p<0.01$) over placebo, in terms of an improved recovery profile.

Memory



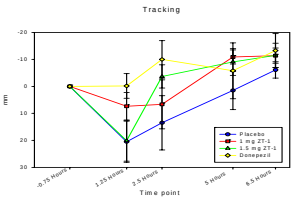
Positive effects of ZT-1 were also seen in episodic secondary memory and working memory, this time expressed in terms of the ability to reverse the effects seen 0.75 hours after the administration of scopolamine.

Reduction of the scopolamine's impairment was significant for both doses of ZT-1, as well as donepezil in the Word Recall test.



The figure for Spatial Working Memory Speed showed clear benefits for 1.5 mg ZT-1 and donepezil at 1.25 and 2.5 hours, which persisted for 1.5 mg ZT-1 at 5 and 6.5 hours, whilst donepezil declined slightly.

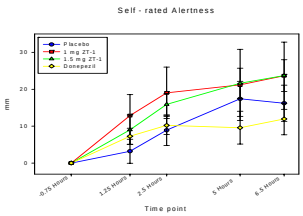
Eye-hand coordination



The figure for the Tracking task showed a benefit for 1.5 mg ZT-1 at 2.5 hours.

There was also a less pronounced benefit for 1.0 mg ZT-1 , whilst there was a clear benefit for donepezil.

Mood



The figure for Self-rated Alertness showed a profile of improvement following the initial scopolamine challenge, under all study treatments, across the study. The best profile was seen under the two doses of ZT-1.

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

Ebert U, Oertel R, Wesnes K, Kirch W (1998a). Effects of physostigmine on scopolamine-induced changes in quantitative electroencephalogram and cognitive performance. *Human Psychopharmacology* 13: 199-210.

Wang H, Tang XC. (1998). Anticholinesterase effects of huperzine A, E2020, and tacrine in rats. *Acta Pharmacol Sin*:19:27-30.

Wesnes K, Anand R, Simpson PM and Christmas L (1990b). The use of a scopolamine model to study the potential nootropic effects of aniracetam and piracetam in healthy volunteers. *Journal of Psychopharmacology* 4: 219-232.

Zangara A. The psychopharmacology of huperzine A: an alkaloid with cognitive enhancing and neuroprotective properties of interest in the treatment of Alzheimer's disease. *Pharmacol Biochem Behav.* 2003 Jun; 75(3): 675-86