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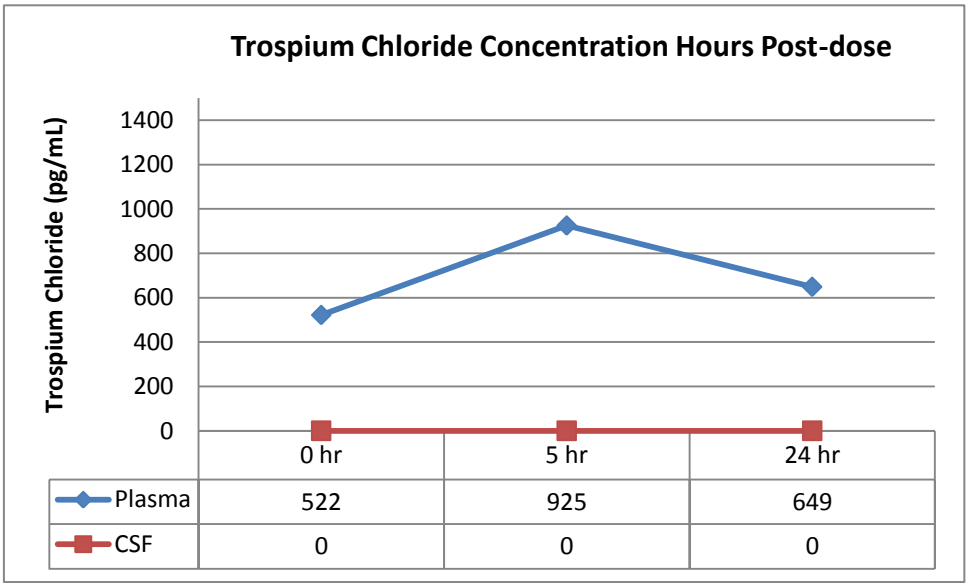
TROSPIUM CHLORIDE-EXTENDED RELEASE (XR) 60 MG ONCE DAILY HAS NO EFFECT ON MEMORY TESTING AND IS ASSAY UNDETECTABLE IN THE CENTRAL NERVOUS SYSTEM OF OLDER PATIENTS WITH OVERACTIVE BLADDER.

Hypothesis / aims of study
To determine if trospium chloride is assay detectable in the CNS of older adults with over active bladder (OAB) syndrome and to assess whether deterioration of memory occurs in these individuals.

Study design, materials and methods
Twelve cognitively intact older adults (≥ 65-75 years old) with OAB provided informed consent and were enrolled in an IRB approved study. Trospium chloride XR 60 mg once daily was administered over a 10-day period to achieve plasma steady state levels. Standardized memory testing (HVLT-R and BVMT-R) was performed pre and post-dose. Cerebrospinal spinal fluid (CSF) and plasma samples were drawn on Day 10 and assayed for trospium chloride. Pre-dose (Day 0) and post-dose (Day 10) results on the memory tests were compared using a reliable change index to assess a meaningful change in learning or memory.

Results
Trospium chloride levels in all the CSF samples (n=72) of all participants were assay undetectable (<40 pg/ml) on Day 10 at steady state peak plasma concentration concurrent with measureable peak plasma values (Cmax=925 pg/mL)(figure). Repeat memory testing revealed no clinically significant net drug effect on learning or recall.



Interpretation of results
This is the first study to investigate for the presence of an OAB antimuscarinic in the human brain, performed by assaying for concentrations of trospium chloride and correlating with simultaneous clinical cognitive safety measures. The results of both pharmacological and neuropsychological testing support the hypothesis of a lack of detectable central nervous system penetration for the quaternary amine trospium chloride.

Concluding message

Based on the quaternary amine structure and the corresponding cationic charge, it has been predicted that trospium chloride would not be able to cross the human Blood-Brain Barrier (BBB). Due to the complexities of the aging human BBB, this concept required human clinical trial validation. The current trial, although small, is the first to

support the lack of trospium chloride penetration in older adults, with OAB and stable co-morbid disease who are at increased risk for drug penetration across the BBB. The correlation of this pharmacokinetic finding with the memory test findings supports the pharmacodynamic antimuscarinic hypothesis—if an antimuscarinic doesn't cross the blood brain barrier it should not cause cognitive impairment. Larger, comparator trials are a logical next step in the evaluation and interpretation of these preliminary findings.

Specify source of funding or grant	**Allergan, LLC**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**NCT00863551**
Is this a Randomised Controlled Trial (RCT)?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Aspire IRB, Le Mesa, CA.**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**