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A PROSPECTIVE RANDOMIZED DOUBLE BLIND CROSS-OVER DOSE-TITRATION STUDY TO EVALUATE THE COGNITIVE SAFETY PROFILE OF TOLTERODINE AS COMPARED TO OXYBUTYNIN IN MULTIPLE SCLEROSIS PATIENTS WITH A NEUROGENIC OVERACTIVE BLADDER : A PLANNED INTERIM ANALYSIS.

Hypothesis / aims of study

Oxybutynin is widely used in the treatment of bladder symptoms in multiple sclerosis. It can cause several side effects, including cognitive dysfunction. Tolterodine is a muscarinic receptor antagonist which does not easily cross the blood brain barrier. For this reason, it should cause less central nervous system side effects.
We performed a double blind cross over trial, in which patients with clinically definite multiple sclerosis were included. Patients had to score 3 or less on the Rao battery (1) a standard cognitive screening battery for multiple sclerosis, and need anticholinergic treatment for bladder dysfunction at screening to be included.

Study design, materials and methods

Patients were randomized to receive either oxybutynin or tolterodine for eight weeks. After eight weeks, patients crossed over to the other medication for another eight weeks. The oxybutynin dose was 2.5 mg TID, and the tolterodine dose was 2 mg BID. The hospital pharmacist was responsible for randomisation. Patients and evaluating neurologist and psychologist were blinded for treatment arm.
Cognitive function was primarily evaluated with the paced auditory serial addition test, or PASAT.
Secondary cognitive endpoint was the ADAS-Cog. Tertiary endpoints included the MACFIMS test battery for multiple sclerosis (2) and the mini mental state examination (MMSE) (3).

Results

Fourteen patients have been included at the time of this interim analysis. Only the first randomisation block of ten patients was considered for this per protocol analysis. Of these ten, three dropped out of the study after screening and randomisation, because they felt the test battery was too cumbersome.
Tolterodine treated patients scored 21 ± 12.8 on average on the PASAT, while oxybutynin treated patients scored 15.7 ± 4.2.
MMSE scores were 26.4 ± 1.3 for tolterodine treated patients and 25.7 ± 2.6 for oxybutynin treated patients.
Tolterodine treated patients on average performed better, but not significantly so on the 7/24 selective reminding test, Cowat and California verbal learning subtests of the MACFIMS.

Interpretation of results

Results of the interim analysis indicate a clear trend towards a better PASAT performance of MS patients under tolterodine than under oxybutynin in a double blind crossover design. The ADAS cog and the MMSE do not appear to have enough sensitivity for clinical trials on cognition in multiple sclerosis.

Concluding message

These results imply less cognitive side effects for tolterodine, compared to oxybutynin in multiple sclerosis patients with a neurogenic overactive bladder.

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