The cognitive safety of bladder antimuscarinics in older persons

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In the last 3 years, I have received monies for either consulting, speaker fees or research from:

- Astellas Pharma
- Pfizer
- SCA
- Watson Pharma

I am President of the Canadian Continence Foundation and a Trustee of the International Continence Society
The problem

The use of drugs with antimuscarinic properties is associated with low cognitive performance among community-dwelling elderly people.

Systematic review of anticholinergic medications and cognition in older people found 27 papers. All except two confirmed an association between serum anticholinergic activity and cognitive impairment. The majority of these studies assessed the nursing home population, nine assessed the association in community dwelling older adults. Most studies short duration without any assessment of health related outcome such as morbidity, hospital admission or death.
Drugs With Anticholinergic Properties, Cognitive Decline, and Dementia in an Elderly General Population

The 3-City Study

- 520/6912 participants (7.5%) were taking anticholinergic drugs at baseline
- 36 participants (6.9%) were taking 2 anticholinergic drugs
- 8 (1.5%) were taking 3 drugs.
- 1.6% of the participants were taking bladder drugs
women reporting use of anticholinergic drugs at baseline showed greater decline over 4 years in
   – verbal fluency scores (odds ratio [OR], 1.41; 95% confidence interval [CI], 1.11-1.79)
   – global cognitive functioning (OR, 1.22; 95% CI, 0.96-1.55)
• In men, decline in
   – visual memory (OR, 1.63; 95% CI, 1.08-2.47)
   – executive function (OR, 1.47; 95% CI, 0.89-2.44).

• A 1.4- to 2-fold higher risk was observed for those who continuously used anticholinergic drugs but not for those who had discontinued use.

• The risk of incident dementia over the 4-year follow-up period was also increased in continuous users (hazard ratio [HR], 1.65; 95% CI, 1.00-2.73)
Fox et al examined medication use between 1991 – 1993 in 12,423 men and women over the age of 65 years.

The most commonly used drugs in this cohort were furosemide, dextropropoxyphene, atenolol and nifedipine.

Over 2 years, use of medications with anticholinergic properties was associated with:

- greater decline (0.33 points, 95%CI 0.03 – 0.64) in MMSE score than those not taking anticholinergics.
- mortality was greater for those taking medications with definite anticholinergic properties (OR 1.68; 95% CI 1.30 – 2.16).

• Retrospective cross sectional study of cognition in 134 people, (mean age 79 years), found an association between the number of drugs with anticholinergic properties and impairment of verbal episodic memory.

• most commonly prescribed anticholinergic drugs were furosemide, hydrochlorothiazide, digoxin, fluoxetine, paroxetine, sertraline and oxybutynin.

Polypharmacy in the ED

No of drugs

% patients

N=340

30 – 50% of drugs prescribed for older people have anticholinergic effects

10% older people with dementia in clinics prescribed new anticholinergic agent

Older people with dementia significantly more likely to take anticholinergic agent than cognitively intact elderly

Tune L et al. The American Journal of Psychiatry, 1992;149:1393-4
Serum anticholinergic levels ranked according to frequency of prescriptions in older adults

Medications with the five highest levels of anticholinergic activity:

- Furosemide*
- Digoxin*
- Dipyridamole
- Dipyridamole
- Theophylline*
- Dyazide
- Dipyridamole
- Theophylline*
- Warfarin
- Prednisolone*
- Nifedipine*
- Isosorbide dinitrate
- Codeine
- Cimetidine*
- Captopril
- Ranitidine*

*Medications with the five highest levels of anticholinergic activity.

Anticholinergic activity and common drugs

High >15 pmol/L
- Amitriptyline
- Doxepin
- Clozapine
- Atropine
- Dicyclamine
- Tolterodine

Moderate 5 – 15pmol/L
- Nortriptyline
- Paroxetine
- Chlorpromazine
- Olanzapine
- Oxybutynin

Mild 0.5 – 5 pmol/L
- Citalopram
- Escitalopram
- Fluoxetine
- Mirtazepine
- Quetiapine
- Temazepam
- Ranitidine

Adapted from Gerretsen P, Pollock BG Drugs Ageing 2011
Anticholinergic burden and MMSE scores

Community-based sample of older people (n=201)

% subjects with low MMSE score (≤24)

SAA (pmol/mL)

MMSE = Mini-mental state examination
SAA = serum anticholinergic activity
*p<0.05 vs undetectable SAA (logistic regression)

Muscarinic receptors and the central nervous system

• Cholinergic neurons are widespread throughout the brain
  – all five muscarinic receptors are expressed
  – varying amounts
  – various locations
  – highest density found in the striatum and the hippocampus
• The cholinergic system has a widespread influence on learning and cognition, attention and memory
• Cholinergic receptor blockade impairs these processes
M1 receptor is the commonest post synaptic receptor with M2 being largely pre-synaptic.

Cerebral cortex M1 predominant

basal forebrain M2>M1

striatum, 50% presynaptic M4, 50% pre-synaptic M1
cholinergic system modulates stimulus processing

- Working memory, the temporary retention of images or stimuli for late processing or recall is strongly affected by the cholinergic system
- essential in the maintenance of attention,
- discrimination between important and irrelevant stimuli
- resolve potential conflict when there is competition
- cognitive dysfunction seen in CNS M1 & M2 knockout mice
• damage or abnormalities in the cholinergic pathways relate to cognitive decline.

• cholinergic blockade produces memory effects similar to those commonly observed in non-demented elderly subjects,

• Blockade of muscarinic receptors may promote tau protein phosphorylation, part of the pathology of AD.

• cholinergic loss associated with normal ageing....
Periventricular white matter hyperintensities

- Studies in the community-dwelling elderly link structural white matter changes in the brain with:
  - Mobility impairment
  - Cognitive impairment
  - Urinary urgency
  - Urinary incontinence

- Elderly individuals with greater white matter hyperintensity burden also show increased prevalence of detrusor overactivity and difficulty maintaining continence on urodynamic studies

Association between decreased cholinergic activity and increasing periventricular white matter hyperintensities

• The ability of any anticholinergic agent to have an effect on the CNS and cognition depends upon:
  – Affinity for the muscarinic Ach receptors in the CNS, particularly M1 receptor
  – The permeability across the blood–brain barrier, (affected by molecular size, lipophilicity, and chemical charge of the agent)
  – Whether or not the drug is a substrate for the p-glycoproteins which actively transport the drug from the CNS
Anticholinergic activity

- Tolterodine
- 5-HMT
- Oxybutynin
- Solifenacin
- Darifenacin
- Propiverine
- Trospium

BBB (kPi for M1)

Bladder antimuscarinics and the blood brain barrier

- Darifenacin
- 5-HMT
- Trospium

P-glycoprotein active transport

Drug penetration and activity

- in vitro brain anticholinergic activity highest in
  - 5-HMT (the active metabolite of tolterodine and fesoterodine)
  - tolterodine
- this was more than 10 times higher than oxybutynin, solifenacin, and darifenacin

Time course effects of oral oxybutynin (0.3mg/kg) on [11C](+)3-MPB binding to muscarinic receptors in the brain of conscious monkey as measured by PET

Life sciences, 2010;87:175-80, Maruyama S et al. Incontinence Society Meeting 2007; poster number 79.
What is known about drugs for the bladder?

• Data exist for the following drugs in cognitively intact older adults
  – darifenacin
  – solifenacin
  – oxybutynin transdermal gel
  – tolterodine
  – trospium chloride
  – fesoterodine

• In older adults with mild cognitive impairment
  – solifenacin

Eur Urol 2006;50:317-26
NeuroUrol Urodyn 2009;28:711-712
36th Annual Meeting of the ICS, Christchurch, New Zealand, December 2006:Abstr 87
12 pts, >65, cognitively intact
Standard cognitive battery
Single 10mg dose
decline in mean values for Quality of Working Memory at 2 and 4 h post-dose with solifenacin
the decline was less than that seen with oxybutynin
by 6 h post-dose the effects of solifenacin on this parameter were similar to placebo
• 129 pts >65
• Cognitively intact
• 14 days therapy, 7 days washout
• There were no statistically significant differences compared to placebo
• for the mean change from baseline in memory scanning sensitivity, speed of choice reaction time and word recognition sensitivity.
• 17 subjects, >65, cognitively intact

• Tolterodine ER (4 mg) had no effect on the primary outcome measure (delayed recall on the Name-Face Association Test) or on other measures in the cognitive function test battery at any time point.

• no decline, relative to baseline, in cognitive test performance for subjects taking tolterodine ER.

• Significant decline in delayed recall on the Name-Face Association Test for oxybutynin ER 20 mg.
• 152 subjects, mean age 68.2, cognitively intact
• 1 weeks therapy
• Primary endpoint, Name-Face Association delayed recall, showed no significant treatment effect (p=0.273).
• The Misplaced Objects Test showed a significant treatment effect (p=0.023), with placebo and OTG scores both improving and OXY-IR decreasing
• Analysis of Reliable Change scores in the HVLT-Total Free Recall (i.e., a decline ≥ 6 from Baseline) indicates that 10 subjects showed a significant decline on OXY-IR, 6 subjects on Placebo and 5 subjects on OTG.
• 12 subjects, cognitively intact, chronic dosing

• No total or delayed recall individual HTLV-R score indicated a significant decline in learning or memory on trospium chloride.

• No measurable trospium (<40 pg/ml) was found in CSF at any sampling time in any subject.
To evaluate the cognitive effects of fesoterodine in healthy older adults

Randomized, positive (alprazolam)- and placebo-controlled, double-blind, double-dummy, 4-way crossover study

18 subjects were included in the per protocol analysis set

The study comprised 4 treatment periods (separated by 3-6 day washout periods):

- Fesoterodine 4 mg for 6 days with alprazolam-matching placebo on Day 6
- Fesoterodine 4 mg for 3 days, followed by fesoterodine 8 mg for 3 days with alprazolam-matching placebo on Day 6
- Placebo for 6 days with alprazolam-matching placebo on Day 6
- Placebo for 6 days with alprazolam 1 mg on Day 6
Detection Task (Primary endpoint)

Identification Task

1-Card Learning Task

Mean change from baseline to day 6

Continuous Paired Association Learning Task

Groton Maze Learning Test

Rey Auditory Verbal Learning Test

Patients with an increased risk of cognitive deficit

- Alzheimer's disease and related dementias (including mild cognitive impairment, age-associated memory impairment)\textsuperscript{1}
- Parkinson’s disease\textsuperscript{2}
- Type 2 diabetes in the elderly\textsuperscript{3}
- poorly controlled hypertension\textsuperscript{4}
- Multiple sclerosis\textsuperscript{5}
- Alcohol dependence\textsuperscript{6}

5. Gaudino EA et al. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14: 32–44.
Solifenacin in people with MCI

- Primary endpoint was change from baseline in cognitive function with solifenacin at 6 h and oxybutynin at 2 h post dose.
- Secondary endpoints:
  - change in cognitive function at additional time-points
  - safety and tolerability assessments.
- Neither agent was associated with significant changes from baseline in any of the five standard composite outcomes of cognitive function.

• At the 1 + 2 h time point, there were statistically significant decreases in power of attention ($p = 0.037$) and continuity of attention ($p = 0.002$) comparing oxybutynin versus placebo.

• Power of attention was statistically significantly increased with oxybutynin versus placebo at the pooled 4 + 6 h time point ($p = 0.047$).

• Oxybutynin was associated with a statistically significant decrease in self-rated alertness versus placebo at the pooled 1 + 2 h timepoints.

Impact of Cholinesterase inhibitors

Dual Use of Bladder Anticholinergics and Cholinesterase Inhibitors: Long-Term Functional and Cognitive Outcomes

Kaycee M. Sink, MD, MAS,* Joseph Thomas, III, PhD,†† Huiping Xu, PhD,§ Bruce Craig, PhD,§ Steven Kritchevsky, PhD,* and Laura P. Sands, PhD‡‖

• Examined the cognitive and functional consequences of dual use of CHIs and oxybutynin or tolterodine¹

• In residents in the top quartile of ADL (Activity Of Daily Living) function, a 50% greater rate in quarterly decline¹

• No delirium¹

• RCT needed – no continence outcomes

46 subjects with UI and dementia
Galantamine and trospium chloride
10 withdrew from the study
No effect on cognition or activities of daily living was detected over 6 months
A within group analysis demonstrated an improvement in nocturia and reduction in pad use in this combination group

Dementia, urgency incontinence and cholinesterase inhibitors

- Twenty-six cognitively impaired older individuals
- 7 men, 19 women, mean age 78 (range 62–88)
- Donepezil 5mg
- 20mg propiverine hydrochloride
- Daily incontinence disappeared in 36% of patients
- no correlation between the changes in urinary symptoms and age, sex, underlying disease, gait function, or MMSE

MMSE Score change from Baseline similar after treatment with Fesoterodine and placebo after 12 Weeks

- Three patients in the Double Blind Phase Fesoterodine arm discontinued treatment due to cognitive function impairment:
  - 1 patient discontinued fesoterodine due to cognitive problems (related),
  - 1 patient discontinued due to amnesia (unrelated)
  - 1 patient discontinued due to confusional state (unrelated).
For antimuscarinic agents in the elderly:

- Single antimuscarinic agents may be comparatively safe
- Combinations, a high antimuscarinic load, may not be
- Long exposure times may be undesirable
- In cognitively intact older people, for the majority of antimuscarinics, no effect on cognition can be identified in the short term
- In older people with MCI, no adverse effect of solifenacin (versus placebo)
- There may be an indication for dual Rx with AChEI in patients with a dementia diagnosis
- In clinical trials assessing MMSE, no effect detectable