Inhaled Anticholinergics and Risk for Acute Urinary Retention: a Case-Crossover and Case-Time-Control Study

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Background

- Inhaled anticholinergic agents, such as ipratropium and tiotropium (long-acting), are widely used in chronic obstructive pulmonary disease (COPD). Both have been shown effective in relieving symptoms while tiotropium also reduces the number of exacerbations.1
- FDA-approved label change of tiotropium in December 2005, to warn the risk of worsening for urinary retention and complications of prostate (prostate hyperplasia or bladder-neck obstruction).
- Recent nested case-control studies have tested the association of the risk of acute urinary retention (AUR) among patients receiving tiotropium.2,3
- More evidence is needed to understand the safety in use of inhaled anticholinergics. Self-controlled methods can provide a unique and valued study approach which adjusts for all intra- and inter-subject variability (measured and unmeasured) and reduces threat of control-selection bias.

Objective

To examine the effect of inhaled anticholinergics on the occurrence of AUR using self-controlled methods, case-crossover (CCO) and case-time-control (CTC) designs

Methods

- Patients aged 45 years and COPD diagnosis (ICD-9 codes 491, 492, 496) were included from the IMS LifeLink Center of Pharmaceutical Outcomes Research, Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL, USA;
- Cases with AUR (ICD-9 diagnosis code 782.82 [excluding 782.82] or 599.6) in both inpatient and outpatient settings were identified.
- To select only primary AUR cases, the index date for cases was defined as the first AUR in each individual that allows a 12-month event-free observation time prior to its occurrence.
- Patients were excluded if they were diagnosed with conditions such as bladder cancer, urethral stricture, urinary incontinence, or received radical cystectomy prior to the index event (for cases) or during data available period for external controls (in the case-time-control design).
- Exposure to ipratropium, tiotropium, and medications with significant anticholinergic effects were determined in the 30-day period prior to the event, i.e., period, and in a 300-day period which was 180 days prior (Figure 1).
- Multivariate conditional logistic regression was used to evaluate the association between anticholinergic use and AUR based on:
  - CCO design (cases only): Odds ratios (OR) were derived from within-individual comparisons that compared the odds of exposure within index period vs. the odds of exposure during obesity prior to index period.
  - CTC design, further used time-matched external control cases to eliminate the exposure-bias. Ten controls were randomly selected for each case after matching age, gender, and geographic region. CTC ORs were obtained by dividing the CCO OR by the OR for the time trend of medication exposure.
  - We also adjusted for confounding use of medications with strong anticholinergic properties.
- Sensitivity analyses:
  - Subgroups with higher risk—elderly, males, and patients with benign prostatic hyperplasia (BPH), prostate cancer, diabetes mellitus (DM), and neuropsychiatric impairment.
  - Different length of exposure time window (for both case and relevant periods): 7, 14, and 60 days.

Results

- A total of 6,008 cases and 60,080 controls were identified. The mean age was 74 years and 78% were male (Table 1).
- Compared to the external controls, cases with AUR were more likely to have BPH, prostate cancer, DM, and neuropsychiatric impairment (Table 1).
- The ORs of AUR decreased toward one when a shorter exposure window (i.e., 7, 14 days) was used for the case and relevant periods (Table 2). However, there was a consistent trend of elevated risk associated with the inhaled anticholinergics.
- Our results support current evidence that use of inhaled anticholinergics is associated with higher risk for AUR (ips) compared with COPD patients (measured and unmeasured) and reduces threat of control-selection bias.

Conclusions

- The CCO and CTC study can efficiently eliminate the confounding effect from all time-imparted factors and thus provide an alternative approach and evidence in addition to the results from the population-based case-control studies.

References