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## Effect of daily tiotropium on allergen-induced early asthmatic responses and airway inflammation



Long-acting muscarinic antagonists (LAMAs) have been approved as an add-on treatment for moderate-to-severe asthma—tiotropium as an individual inhaler and umeclidinium as a combination inhaler. Data from ovalbumin-sensitized and challenged animals treated with muscarinic antagonists, including tiotropium, reveal reductions in inflammatory markers and allergen-associated changes.<sup>1,2</sup> Inhaled muscarinic antagonists may, therefore, protect the airways of patients with allergic asthma through both bronchodilators (ie, decrease the early asthmatic response [EAR]) and anti-inflammatory action (ie, decrease type 2 [T2] eosinophilic airway inflammation). Single-dose short-acting muscarinic antagonists (eg, ipratropium) partially inhibit allergen-induced EARs in human studies.<sup>3,4</sup> There are no human data on LAMA efficacy against allergen-induced asthmatic responses. Here, we report the results of a pilot investigation of the efficacy of regular use of tiotropium on the allergen-induced EAR and T2 eosinophilic airway inflammation.

A total of 13 stable patients with mild atopic asthma, requiring only infrequent, as-needed salbutamol, with forced expired volume in 1 second (FEV<sub>1</sub>) greater than or equal to 80% predicted (7 men, ages 31 ± 0.2 years, height 171.3 ± 8.3 cm, FEV<sub>1</sub> 92.7 ± 7.0% predicted) completed this double-blind, placebo-controlled, randomized, crossover trial. Participants inhaled 8 once-daily doses of tiotropium (Spiriva, Respimat) 5 µg (2.5 µg × 2 puffs) or an identical-appearing placebo with a 14-day washout. A standardized allergen inhalation test<sup>5</sup> was performed 30 minutes after the last dose of each treatment. Doubling doses of allergen (cat n = 8, mite n = 4, grass n = 1 [Omega laboratories, Montreal, Québec, Canada]) were inhaled with an Aerogen Solo vibrating mesh nebulizer (Canadian Hospital Specialties Ltd, Oakville, Ontario, Canada) at 12-minute intervals until a 20% fall in FEV<sub>1</sub> was achieved. Monitoring of FEV<sub>1</sub> was done thereafter for 5 hours and the EAR allergen provocation dose causing a 20% fall in FEV<sub>1</sub> (EAR PD<sub>20</sub>) within the first hour was determined. Airway response to methacholine (MCh PD<sub>20</sub>),<sup>5</sup> FEV<sub>1</sub>, and induced sputum eosinophil count (sputum eosinophil %)<sup>6</sup> were measured before the first dose of each treatment, and sputum eosinophil % was repeated 5 hours after allergen inhalation. The MCh PD<sub>20</sub> and allergen EAR PD<sub>20</sub> were log-transformed before analysis. Student's paired *t* test was used to compare the baseline FEV<sub>1</sub>, baseline MCh PD<sub>20</sub>, baseline sputum eosinophil %, the 2 allergen EAR PD<sub>20</sub>s, and the change in sputum eosinophil % from baseline to 5 hours after allergen exposure.

All 13 participants completed the study with no adverse events. There was no difference in mean baseline FEV<sub>1</sub> (*P* = .21), baseline geometric mean MCh PD<sub>20</sub> (*P* = .63), or baseline sputum eosinophil % (*P* = .16) before the 2 treatments. At baseline, there was no correlation between predicted FEV<sub>1</sub> and log sputum eosinophils (*P* = .25). Allergen EAR PD<sub>20</sub>s are illustrated in Figure 1. After tiotropium, allergen responsiveness increased; the geometric mean PD<sub>20</sub> was lower compared with placebo (16.7 and 22.2 allergen units respectively, 0.41 doubling doses [*P* = .054]). Individually, 10 of 13 participants exhibited a greater posttiotropium fall in allergen EAR PD<sub>20</sub> compared with placebo, 2 of which had a fall of greater than 1 doubling dose. The sputum eosinophil percentage increased in 8 participants who were able to produce sputum after both allergen challenges (5.7% to 19.7% for placebo [*P* = .002] and 3.8% to 18.3% for tiotropium [*P* = .01]) with no significant difference between the 2 treatments (*P* = .91).

In our study of 13 patients with well-controlled mild allergic asthma, the daily use of tiotropium for 8 days led to a borderline significant increase in the allergen-induced EAR (*P* = .054) with no significant effect on allergen-induced sputum eosinophilia (*P* = .91). We hypothesized that tiotropium, much like ipratropium, would elicit at least minor protection against allergen-induced EARs because of a bronchodilator, functional antagonist effect, with or without an additional anti-inflammatory effect. We cannot rule out the possibility that regular use of tiotropium may have induced the increased responsiveness to the allergen, an effect seen with regular β<sub>2</sub>-agonist use along with tolerance to the bronchoprotective effects vs both allergen (EAR) and methacholine responses.<sup>7</sup> However, the regular use of ipratropium bromide (40 µg thrice daily for 7 days) does not produce tolerance to the bronchoprotective effect against methacholine,<sup>8</sup> and preliminary data from an ongoing double-blind study of regular LAMA use on bronchoprotection to methacholine seems to be generating a similar outcome. An alternative explanation for increased allergen responsiveness after tiotropium could relate to enhanced mast cell degranulation. Tiotropium, despite being kinetically selective for M<sub>3</sub> receptors, retains substantial binding affinity for the M<sub>1</sub> receptor. Acetylcholine released from proximal nonneural cells inhibit mast cell histamine release by means of M<sub>1</sub> stimulation.<sup>9</sup> Therefore, removal of cholinergic regulated inhibition of mast cell histamine release with regular use of tiotropium may have contributed to the slight enhancement of the EAR we observed. This is a hypothesis to be tested in future studies.

Our negative findings regarding T2 eosinophilic airway inflammation contrast with those of animal models. We recognize our findings could have been influenced by studying predominantly isolated early responders in which a higher dose of allergen may have been administered to induce the EAR after active treatment. If this were the case,

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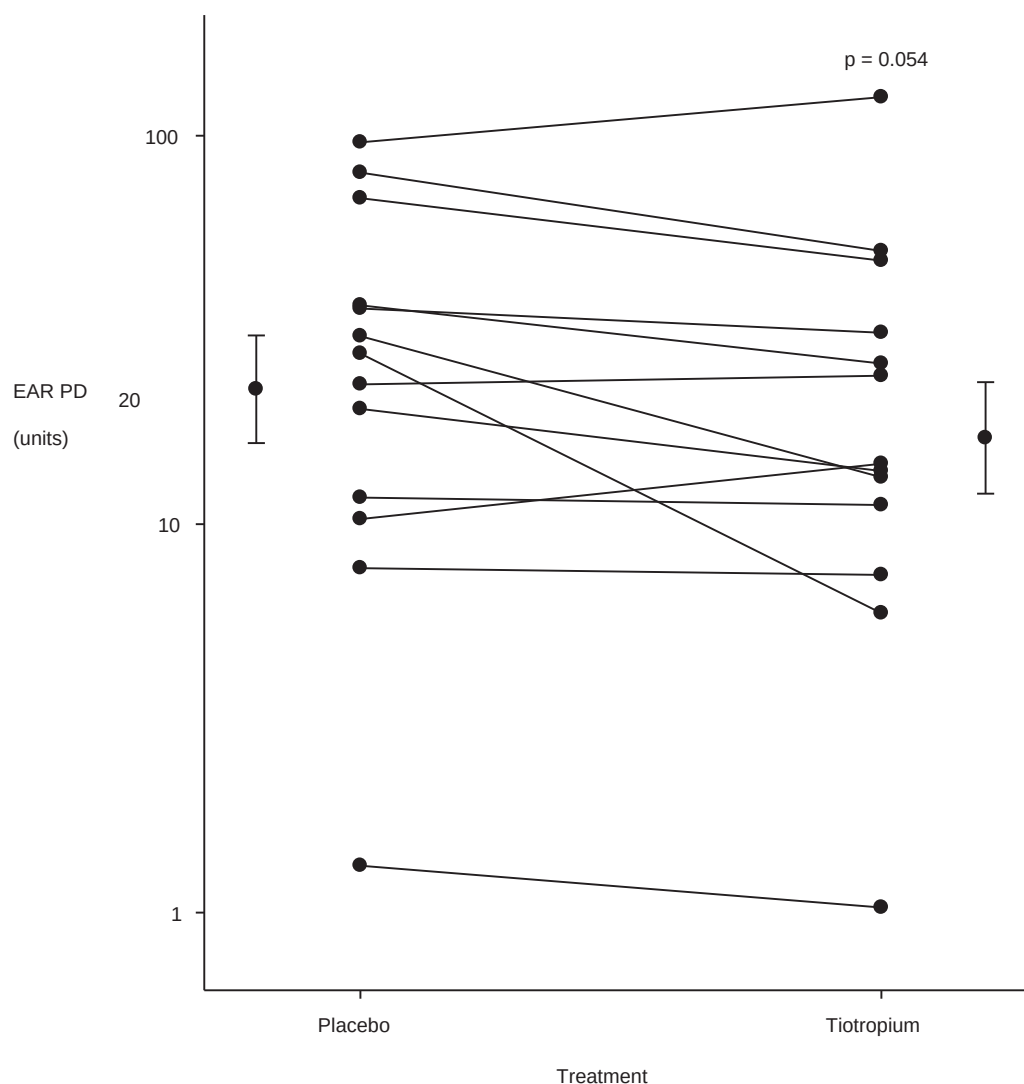


**Figure 1.** Individual and geometric mean allergen EAR PD<sub>20</sub> data after placebo and tiotropium treatments. EAR, early asthmatic response; PD<sub>20</sub>, allergen provocation dose causing a 20% fall in FEV<sub>1</sub>.

administration of a larger dose of allergen after tiotropium treatment may have led to a higher level of airway inflammation, thus, negating any inhibitory effect. However, of the 8 sputum producers, 4 received essentially the same dose of allergen, and 4 received a lower dose of allergen yet all but 1 exhibited marked allergen-induced sputum eosinophilia after tiotropium treatment.

One study limitation that could result in underestimating tiotropium efficacy relates to the unobserved administration of treatment doses 2 through 7. However, all participants were trained in proper dosing techniques and verbally confirmed compliance with daily dosing requirements; postdosing review of device dose counters was also consistent with doses having been administered as required.

Another consideration regarding study limitations, especially with respect to a negative study, relates to study power and sample size. Sample sizes of 13 and 8 in a randomized, double-blind, crossover design provide greater than 80% power to detect a doubling dose shift in EAR PD<sub>20</sub> and 50% reduction in sputum eosinophils, respectively.<sup>10</sup>

On the basis of the present findings, regular use of tiotropium does not prevent allergen-induced bronchoconstriction or alter T2 eosinophilic airway inflammation in a population of those with mild

allergic asthma. The lack of consistency between our current data and the existing human and animal model data are unclear. Further investigation is required.

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## Safety of cefazolin for perioperative prophylaxis in patients with penicillin allergy labels



Cefazolin is a first-line antibiotic for perioperative prophylaxis of surgical site infections.<sup>1</sup> Between 8% and 15% of the US population have penicillin allergy labels (PAL).<sup>2</sup> Patients with PAL receive perioperative cefazolin less frequently and are more likely to receive alternative antibiotics, increasing their risk of surgical site infection.<sup>1</sup> This practice is likely from overestimating the risk of cross-reactivity between penicillin and cephalosporins. Cross-reactivity among these antibiotics is thought to be from a common R1 side chain, absent in cefazolin. Recent studies have found that cross-reactions rarely occur.<sup>3</sup> In a meta-analysis, the rate of cross-reactivity of penicillin with cefazolin was 0.7%.<sup>4</sup> Furthermore, PALs often include intolerances, adverse effects, or reported childhood allergies, which often resolve by adulthood.<sup>3</sup> We hypothesize that cefazolin is safe to use in most patients with PAL. In this study, we aim to learn on the use of cefazolin in patients with PALs, a population typically encountered by clinicians in the perioperative setting who may not have confirmed immunoglobulin E-mediated penicillin allergies.

Patients with PAL at the University of Washington Medical Center (UWMC) who underwent surgical procedures from January 1, 2020 to December 31, 2020 were studied through direct query of the electronic medical record. Data recorded included dates, times, locations, and perioperative antibiotics. Demographics, including age, sex, race, ethnicity, penicillin allergy (PA), and cephalosporin allergy status, were extracted. Procedures in patients with PAL who received cefazolin perioperatively were identified for further review. The PA index reaction and type of penicillin the patient reacted to were identified by manual chart review. When patients had multiple index reactions, all were recorded. Anesthesia and operative notes were reviewed for any documented perioperative reactions. For procedures in which an apparent allergic reaction occurred, an additional review of reaction type, timing of cefazolin administration, concurrent medications given, postoperative clinical notes, and subsequent allergy evaluation (when applicable) was completed. The final determination of whether a reaction was attributable to cefazolin was made by an allergy attending physician. This project was approved by the UWMC institutional review board. All data were recorded in a standardized data collection form in Research Electronic Data Capture.<sup>5</sup>

Of the 16,628 procedures performed at UWMC facilities in 2020, 1741 (10.4%) were for patients with PAL, and 549 (31.5%) of these cases used perioperative cefazolin. Patient demographics and outcomes are described in Table 1. The 549 procedures identified for manual chart review occurred in predominantly white (424, 77.2%) and female (340, 61.9%) patients, similar to procedures in patients with PAL who did not receive cefazolin (1398, 80.3% white; 1113, 63.9% women). Among these procedures, patients with PAL most typically reported a reaction to all penicillins (287, 52.3%), amoxicillin (157, 28.6%), or amoxicillin-clavulanate (76, 13.8%). Some patients reported allergies to multiple penicillin types, and all were recorded (583). Of these procedures in which patients with PAL had index reactions documented (427, 77.8%), the most common were rash (171, 40.0%), gastrointestinal upset (108, 25.3%), or hives (88, 20.6%). A small percentage of patients reported more severe index reactions such as respiratory distress (8, 1.9%), anaphylaxis (5, 1.2%), or angioedema (3, 0.7%). Through manual chart review, 544 (99.1%) of patients with PAL who received cefazolin were found to have no documented allergic-type reaction postoperatively.

Of the 549 cases, 5 involved patients with PAL experienced allergic-type symptoms, none of which seemed related to cefazolin administration. Cases 1 and 2 had index reactions of rash and developed postoperative pruritus 4 hours after cefazolin was given. These reactions were thought most likely related to opioid medication given near the end of the cases. Case 3 had an index reaction of rash and hives and had intraoperative anaphylaxis. Cefazolin had been given 3 hours earlier. Case 4 had an index reaction of rash and developed postoperative pruritus and rash. The cause of this reaction is unknown; however, cefazolin was given 2.5 hours beforehand and did not cause an immediate reaction. Case 5 had an index reaction of rash and developed intraoperative anaphylaxis 15 minutes after cefazolin administration. On outpatient evaluation, this patient had skin testing negative to cefazolin and penicillin, and positive to rocuronium which had been given immediately before the reaction. Therefore, in each of these 5 cases, reactions were thought to be unrelated to cefazolin.

Overall, of all procedures performed in patients with PAL who were given perioperative cefazolin (549, 31.5%) at our institution, none resulted in allergic symptoms related to cefazolin administration. This suggests that cefazolin is safe to give as perioperative prophylaxis in patients with PAL, as seen in similar studies.<sup>6,7</sup> The percentage of cases in which cefazolin was given to patients with PAL was higher than other recently published studies, which reported

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