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Tiotropium Bromide/Olodaterol Related Acute Cognitive Impairments

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Abstract

Background: The use of anticholinergics has been on the rise. With the increase in population longevity, more medication-related cognitive impairments (ACIs) have been reported. These impairments result in significant morbidities. We present a case that stresses on the importance of being vigilant when prescribing anticholinergic medications, especially in the elderlies. **Case Report:** A case of ACIs related to the use of tiotropium bromide/olodaterol (*Stiolto Respimat*) is being reported in a 71-year-old white man with COPD. Treatment with budesonide 180 mcg/actuation, and tiotropium bromide/olodaterol (*Stiolto Respimat*) inhalers was initiated. Two days after initiating treatment, the patient developed ACIs which manifested by gait imbalance, short-term memory dysfunction, inability to remember his family members, or to take his medications. Tiotropium bromide/olodaterol (*Stiolto Respimat*) was discontinued. After three days, a full recovery of ACIs was reported. A month later, due to worsening dyspnea, the patient self-resumed the medicine. Similar ACIs were reported within two days of resuming treatment. Tiotropium bromide/olodaterol (*Stiolto Respimat*) was discontinued indefinitely. Full recovery of ACIs was reported. **Conclusion:** ACIs should be noted as a significant side effect of tiotropium bromide/olodaterol. Clinicians should be vigilant, when prescribing anticholinergic medications to elderlies.

Keywords

Cognitive Impairment, Stiolto, Tiotropium Bromide/Olodaterol, COPD

1. Introduction

Tiotropium bromide/olodaterol (*Stiolto Respimat*) is a long acting anticholinergic and a beta$_2$-adrenergic agonist inhaler, which is indicated for the long-term,

once-daily maintenance treatment of patients with chronic obstructive pulmonary disease (COPD) [1] [2]. The elderlies are particularly vulnerable to anticholinergic-related acute cognitive impairments (ACIs). A case of anticholinergic-related ACIs related to the use of tiotropium bromide/olodaterol (*Stiolto Respimat*) is being reported. A recent review of the literature indicates that such an adverse effect has not been reported. No similar reports were found in the literature which makes this case helpful to add new information to the medical literature.

2. Case Report

A 75-year-old white man, with a history of 20 pack-year smoking and COPD, presented with exertional dyspnea. Past medical history was significant for diabetes, and COPD. Medications were albuterol, and metformin. There was no history of allergies, or alcohol abuse. Physical examination was remarkable for decreased breath sounds bilaterally. Chest radiograph showed signs of hyperinflation. Laboratory values were normal except for a HbA1C of 7.2% (normal range ≤5.7%). Spirometry showed moderate COPD, with a 32% improvement with bronchodilators use.

There were no contraindications to use of tiotropium bromide/olodaterol (*Stiolto Respimat*) such as, heart disease, hypertension, a history of seizures, thyroid disorders, glaucoma, kidney disease, or enlarged prostate/urination problems. Treatments with budesonide 180 mcg/actuation, and tiotropium bromide/olodaterol (*Stiolto Respimat*) inhalers were initiated. Two days after initiating treatment, the patient developed gait imbalance, short-term memory dysfunction, difficulties remembering his family members, or taking his medications. Mini-Mental Status Examination could not be performed. Treatment with tiotropium bromide/olodaterol (*Stiolto Respimat*) was discontinued. After three days, a full recovery of ACIs was reported. A month later, due to worsening of dyspnea, the patient self-resumed treatment with tiotropium bromide/olodaterol (*Stiolto Respimat*). Similar ACIs were reported within two days of medications use. Tiotropium bromide/olodaterol (*Stiolto Respimat*) was discontinued indefinitely. Full recovery of ACIs was reported.

The application of Naranjo scale revealed a score of eight, indicating a probable adverse drug effect (**Table 1**) [3]. The use of the World Health Organization-The Uppsala Monitoring Center system for standardized case causality assessment revealed a casualty term of "certain" (**Table 2**) [4].

3. Discussion

3.1. Anticholinergics

Acetylcholine blocking agents are commonly prescribed. The elderlies have higher exposure to anticholinergics, and they are more vulnerable to anticholinergic-related ACIs [5] [6].

In addition, aging is accompanied by a decline in hepatic and renal drugs

Table 1. Naranjo algorithm. [3]

	Yes	No	Do not know or not done	Our patient
(1) Are there previous conclusive reports on this reaction?	+1	0	0	0
(2) Did the adverse events appear after the suspected drug was given?	+2	−1	0	+2
(3) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	+1
(4) Did the adverse reaction appear when the drug was readministered?	+2	−1	0	+2
(5) Are there alternative causes that could have caused the reaction?	−1	+2	0	+2
(6) Did the reaction reappear when a placebo was given?	−1	+1	0	0
(7) Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	0
(8) Was the reaction more severe when the dose was increased, or less severe when the dose was increased?	+1	0	0	0
(9) Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
(10) Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Totals				8

>9: definite adverse drug reaction; 5 - 8: probable adverse drug reaction; 1 - 4: possible adverse drug reaction; 0: doubtful adverse drug reaction.

Table 2. WHO-UMC causality categories. [4]

Causality term	Assessment criteria	Yes/No
certain	Event or laboratory test abnormality, with plausible time relationship to drug intake.	Yes
certain	Cannot be explained by disease or other drugs.	Yes
certain	Response to withdrawal plausible (pharmacologically, pathologically).	Yes
certain	Event definitive pharmacologically or phenomenologically (*i.e.*, an objective and specific medical disorder or a recognized pharmacological phenomenon).	Yes
certain	Rechallenge satisfactory, if necessary.	Yes
	Final outcome	Certain

clearance, decrease in central nervous system (CNS) cholinergic activities, and an increase in the blood brain barrier (BBB) drugs permeability [5] [6]. Although studies in rats have shown that tiotropium bromide/olodaterol does not cross the BBB [2], this has not been evaluated in humans.

Acetylcholine is an important neurotransmitter in the brain. Muscarinic acetylcholine receptor antagonists induce state-dependent ACIs [7]. Anticholinergics have been suggested to disturb neural networks involved in learning and memory, decrease levels of brain phosphatidycholine, and increase the formation of β-amyloid [8]. Boustani *et al.* developed the Anticholinergic Cognitive Burden (ACB) scale, one of many other cognitive burden assessment scales, as a tool to identify the severity of anticholinergics-related ACIs [5] [6]. The scale ranks anticholinergic activity of medications into four categories, ranging from no anticholinergic activity (=0) to definite/high anticholinergic activity (=3) [5] [6]. Medications with an ACB rating of 1 have an uncertain impact on cognition [5] [6] [9], while those with an ACB rating of 2 or 3 have established, clinically relevant cognitive anticholinergic effects [5] [9]. There is no gold standard for defining medications with anticholinergic effects, and the ACB does not correlate with medication doses [6] [9]. A study by Rudolph et al. validated that higher ACB scores were associated with increased risk of peripheral and central anticholinergic adverse effects [10]. Anticholinergic activities may not arise exclusively from an individual agent with strong anticholinergic effects [9] [11]. Co-prescribing multiple medications with low ACB scores may result in ACB scores of 3 [9] [11].

3.2. Tiotropium Bromide/Olodaterol (*Stiolto Respimat*)

Tiotropium bromide works by inhibiting the action of acetylcholine through muscarinic M3-receptors in bronchial smooth muscles [1] [2]. Each dose (one dose equals two actuations) delivers 5 mcg of tiotropium bromide and 5 mcg of olodaterol [2]. The medicine has a plasma protein binding of 72%, and pharmacokinetics steady state is usually reached by day seven after ongoing therapy [1] [2]. Although it may lead to anticholinergic signs and symptoms at high doses [2], none were reported following a single inhaled dose of 282 mcg of tiotropium bromide in six healthy volunteers [2]. Although, studies in rats have shown that tiotropium bromide does not cross the BBB [2], this has not been evaluated in humans.

3.3. Blood Brain Barrier

BBB has tight junctions (TJs) which prevent paracellular transport of compounds into the brain [12]. TJs can be opened under normal conditions to allow the temporary introduction of compounds into the brain, as well as under pathological conditions, for example, after ischemic stroke [12]. Substances cross the BBB by a variety of mechanisms [13]. One example includes drugs that bind to a protein with the conformation of the protein changes while interacting with capillary walls and a drug molecule is freed from the complex into CNS [14]. Another way is that a drug crosses the BBB through permeable capillaries in which

dense fenestrated capillaries permit free communications between the brain and blood [15], or through a leaky BBB that exhibits increased permeability, such as in the case with people who have cerebral amyloid angiopathy (CAA) [12] [16] [17] [18], or with new openings in TJs like after suffering an ischemic stroke [12].

3.4. Possible Explanations of the Development of ACIs in This Patient Are

1) Tiotropium bromide/olodaterol (*Stiolto Respimat*) may have entered the CNS, after binding to a protein which facilitates the crossing of the BBB [13], direct entry may also occur through areas with fenestrated capillaries [15], leaky BBB secondary to either age-related CAA [5], or through new openings in TJs of BBB that developed after suffering an ischemic stroke [12]. Although this patient does not have a confirmed diagnosis of CAA, he has diabetes which may contribute to the development of CAA [19].

2) Being elderly is associated with a reduction in central cholinergic activities (5), and an increased sensitivity to the development of anticholinergic related ACIs [5]. These associations may explain the development of anticholinergic related ACIs, only after three doses/days of initiating treatment and before reaching a steady state.

4. Conclusions

Tiotropium bromide/olodaterol (*Stiolto Respimat*)-related ACIs have not been reported previously in the literature. Tiotropium bromide/olodaterol (*Stiolto Respimat*) should be considered to have a high ACB score. Prescribers may utilize ACB scale to discuss the potential ACIs related to the use of Tiotropium bromide/olodaterol (*Stiolto Respimat*) in elderlies [5]. Such information should be utilized to assure patients' safety [9]. The ACIs of anticholinergics require further analysis. Healthcare providers should attempt to limit prescribing anticholinergics whenever possible, especially in elderlies [7].

ACIs should be included as an adverse effect of tiotropium bromide/olodaterol (*Stiolto Respimat*) in the regulatory document.

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Author Contributions

We both authors contributed equally to this manuscript.

Declaration about Ethics Approval and Informed Consent Statement

Written informed consent was obtained from the patient for the publication of this case report.

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