Tiotropium Bromide Binding to Muscarinic (M3) Acetylcholine Receptor
Poster Team: Anna Depies, Sean Ford, Tiffany Kremmer, Micaela Pommerning, Megan Shaff, Karina Sundar, and Carolyn Van Straten
Jmil Team: Paul Rosman and Jerry Sulewski

ABSTRACT
Tiotropium bromide (Spiriva®) is a long-acting, inhaled anticholinergic agent used for maintenance of chronic obstructive pulmonary disease (COPD). Tiotropium bromide acts by competitively and reversibly inhibiting muscarinic receptors M1, M2, and M3. This mechanism of action causes bronchodilation and relaxation of smooth muscle in the lungs. The tiotropium bromide molecular structure provides higher binding specificity to the M3 receptor when locally administered. Our goal was to clarify the interactions between the tiotropium molecule and its receptors.

CASE STUDY
A patient presents to the pharmacy with prescriptions for tiotropium bromide and aclidinium bromide (Tudorza®). Both medications are long-acting antimuscarinic inhalation medications for COPD.
- Past Medical History: COPD
- Family History: cardiac disorder
- Patient prefers the drug to be covered by insurance, dosed once daily, and for it not to have a bad taste.

THE MOLECULE

Use & Dosing
- Long-term treatment of bronchospasms and exacerbation reduction associated with COPD
- Tiotropium bromide is available as a once-daily regimen in two different dosage forms:
  - 18 mcg inhalation powder administered via the HandiHaler®
  - 5 mcg inhalation spray administered via the Respimat® Inhaler

Known Adverse Effects
- Tiotropium bromide is limited in systemic absorption (~14%)
- Minimal crossing of the Brain Barrier (BBB) limits additional toxicities
- Any systemic absorption may increase risk of other off-target effects such as:
  - Dry mouth: 4% (spray); 14-16% (powder)
  - Upper respiratory infection (URI): 41-43% (powder only)

MOLECULAR STORY
Optimal Muscarinic Competitive Antagonists Structural Features
R1 and R2: Two large carbocyclic or heterocyclic rings present a conformational change required to signal the G-coupled protein. The rings bind outside the active site, allowing the drug molecule to act as an antagonist.
R3: Increased binding strength due to a hydroxy group forming an extra hydrogen bond with M3.

Important Structural Features of the Molecule and an Alternative Anticholinergic
Tiotropium bromide:
- Two thiopeptide rings increase functional muscarinic receptor selectivity
- Dithienyl derivative of N-methyl scopolamine
- Two methyl groups on nitrogen rather than one (scopolamine)
- Quaternary ammonium
- Epoxide on amino ring
- Six-carbon + 1-nitrogen ring
Aclidinium bromide:
- N-methyl scopolamine moiety replaced with N-phenoxypyropyl (1-azacyclobutyl [2.2.2] octane, resulting in kinetic selectivity for M3 vs M2
- Two thiopeptide rings
- Seven-carbon + 1-nitrogen ring

THE NEXT QUESTION
The HandiHaler® is the original delivery system that uses an encapsulated dry powder dosage form. Delivery of the drug to the lungs requires a specific breathing pattern; complete exhalation of breath, sealing lips around the HandiHaler® mouthpiece, and one slow and deep breath that is strong enough to elevate the powder from the capsule and into the lungs. The FDA recently approved a new dosage form and delivery system of tiotropium bromide, the Respimat® Inhalation Spray. This system is comprised of solution that is delivered in a pre-measured and slow-moving mist, activated by the press of a button. There is no difficult breathing pattern required for delivery of the new formula into the lungs.
Both tiotropium bromide dosage forms are safe and efficacious for preventing exacerbations of COPD. The same active drug is delivered in the two dosage forms, providing selectivity for the M3 receptor and local delivery to the lungs. The two dosage forms also share the same half-life of 5 to 6 days.

Differences between the dosage forms are as follows:
- HandiHaler®
- Respimat®
  - Bioavailability: 19.5% vs 33%
  - Excretion (urine): 14% vs 18.6%
  - Dry mouth: 14-16% vs 4%
  - URI: 41-43% vs 0%

Due to the safety and efficacy of tiotropium bromide, there is no need to modify the molecular structure. Both forms of the drug are administered once daily and only available as name brand, but are relatively affordable for patients.

SUMMARY
The antagonistic action of tiotropium bromide on the M1, M2, and M3 receptors creates an anticholinergic effect in the body. The M3 receptor drug target of COPD is located in the lungs, making inhaled medication a first-line therapy due to quick and local delivery of the drug. Inhibition of the M1, M2, and M3 receptors reduces secretions and airway constriction in the lungs, giving the patient reduced COPD symptoms. We clarified that tiotropium bromide has higher affinity to the M3 receptor which promotes a longer duration of action and limits side effects. Our patient was given tiotropium bromide rather than aclidinium bromide due to the highly specific inhibition of the M3 receptor and the once daily regimen. A Respimat® dosage form was chosen for the ease of use and reduced side effects.

REFERENCES