The pharmacological rationale for the use of inhaled tiotropium in asthma

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Abstract

Tiotropium is an inhaled long-acting anticholinergic, with high M_3 receptor subtype (M_3R) binding affinity, exceedingly half-life at M_3R, and functional selectivity. Molecular mechanisms explain binding to muscarinic receptors, long duration of action, kinetic selectivity, and its role as inverse agonist. Tiotropium inhibit airway smooth muscle M_3Rs leading to bronchodilation. The intracellular signal transduction pathways for the muscarinic regulation of airway smooth muscle tone are complex. There are many molecular pharmacological reasons for combining this inhaled anticholinergic with beta-2-agonists, and potential non-bronchodilator actions of tiotropium were described. The Respimat® Soft Mist™ Inhaler (SMI) is a propellant-free, oral inhalation device, based on an uniblock nozzle system with colliding liquid jets, generating a very fine, slow-moving, long-lasting liquid aerosol. This unique SMI is approved to administer tiotropium bromide in poorly controlled asthma patients. Many pharmacotechnological and pharmacoeducational advantages are discussed, and favourable cost-effectiveness aspects in patients with asthma are mentioned.

Keywords: *tiotropium, pharmacology, soft mist inhaler, asthma*

Rezumat

Argumentele farmacologice pentru utilizarea tiotropiumului inhalat în astm

Tiotropium este un anticolinergic cu acțiune lungă, cu afinitate crescută pentru receptorul M3, subtipul M3R, timp de înjumătățire extrem de lung la nivelul receptorului și selectivitate funcțională. Mecanismele moleculare explică legarea de receptorii muscarinici, durata lungă de acțiune, selectivitatea farmacocinetică și rolul său ca agonist invers. Tiotropium inhibă receptorul M3R din mușchiul neted, inducând bronhodilatație. Căile de semnalizare intracelulară pentru reglarea muscarinică a tonusului musculaturii netede bronșice sunt complexe. Există multiple rațiuni farmacologice moleculare pentru a asocia acest bronhodilatator inhalator cu beta-2-agoniștii, fiind descrise și posibile acțiuni non-bronhodilatatoare ale tiotropiumului. Respimat® Soft Mista Inhaler (SMI) este un dispozitiv de inhalare oral, fără propelant, bazat pe un sistem unibloc cu duză cu coliziune de jeturi lichide, care generează un aerosol lichid foarte fin, cu mișcare lentă, persistent. Acest sistem a fost aprobat pentru administrarea tiotropium la pacienții cu astm necontrolat. Se discută multiplele avantaje farmaco-tehnologice și farmaco-educaționale, ca și beneficiul cost-eficiență la pacienții astmatici.

Cuvinte-cheie: *tiotropium, farmacologie, inhalator cu ceață fină, astm*

The new indication of inhaled **tiotropium Respimat®** in asthma reflects the acceptance by the EU regulatory authorities for the use of tiotropium 5 µg once daily *via* **Soft Mist™ Inhaler** (SMI) as add-on maintenance bronchodilator treatment in adult patients with asthma currently treated with maintenance combination of inhaled corticosteroids (ICS) [≥800µg budesonide/day or equivalent] and long-acting beta$_2$-agonists (LABA) and who experienced ≥1 severe exacerbations in previous year (defined as deterioration of asthma symptoms that requires initiation/at least a doubling of systemic glucocorticoids for ≥3 days), based on the pharmacotherapeutical data of UniTinA-asthma® large-scale programme [1-3]. It should be noted, in order to evaluate the inhaled ocorticosteroid dose, that a metered dose of 400 µg of budesonide in a dry powder reservoir device is equivalent to 320 µg as a delivered dose (at the exit of the mouthpiece)[4].

Tiotropium **molecular features** in favour of using it as an **inhaled anticholinergic** are the quaternary ammonium group involved in non-selective binding to muscarinic receptors (mAChRs) and limiting the systemic bioavailability, and two thiophene rings likely related to functional muscarinic receptor selectivity[5,6].

Tiotropium is an unique, potent, inhaled long-acting muscarinic anticholinergic (LAMA) with high M_3 receptor (M_3R) binding affinity, exceedingly half-life at M_3R (of more than 24 h), and ability to dissociate from M_2R ten times faster than it does from M_3R, reflecting M_3R functional selectivity, a kinetic selectivity for M_3R subtype *vs* M_2R, beneficial probably to minimize M_2R blockade facilitating acetylcholine (ACh) release from parasympathetic nerves and M_2R-mediated heart-related side effects[5-8]. The **molecular mechanism** for the binding of tiotropium to M_3R and M_2R involves binding pocket residues, a deeply buried receptor core with covering lid consisting of three conserved tyrosines. The molecular basis for the long duration of action of tiotropium suggests a highly directed interaction of ligands' hydroxy group with an asparagine residue preventing rapid dissociation *via* a snap-lock mechanism, while molecular basis for the kinetic selectivity involves the extracellular ECL2, near de binding pocket, with greater flexibility in M_2R *vs* M_3R[9]. The molecular mechanism of tiotropium inverse agonism is more complex than stabilization of inactive receptor conformation. Long-term treatment with tiotropium does not induce significant up-regulation of M_3R and tolerance[7].

Tiotropium inhibits airway smooth muscle M_3Rs leading to bronchodilation. Intracellular signal transduction pathways for the mAChRs regulation of airway smooth muscle tone engage: G protein subunits, phospholipase C, diacylglycerol

and inositol trisphosphate, cytosolic calcium, protein kinase C and CPI-17, RhoA and Rho-kinase, myosin light chain kinase and phosphatase. The molecular pharmacological basis for combining inhaled tiotropium with beta$_2$-agonists involves: **(1)** different airway receptor locations, with M_3Rs predominant in more proximal segments and beta-$_2$ adrenergic receptors (b_2ARs) predominant in more distal ones, **(2)** prejunctional b_2ARs enhancing neuronal ACh release, **(3)** privileged intra-cellular signaling cross-talk between receptors, M_3R-induced contraction is more resistant to b_2AR-induced relaxation, M_2Rs limit b_2AR-mediated relaxation *via* adenylate cyclase inhibition, **(4)** chronic cross-regulation of receptor expression and desensitization[10,11]. Potential non-bronchodilator actions of tiotropium were described on epithelial cells, inflammatory cells, airway remodelling, mucus production and cough[12].

Respimat® Soft Mist™ Inhaler is an unique multiple-dose **oral inhalation device**. This propellant-free metered dose inhaler uses mechanical energy from a compressed spring to force tiotropium bromide solution through an uniblock nozzle system with microchannels, to produce two fine liquid jets converging at a preset angle, and colliding to generate a very fine, slow-moving, long-lasting liquid aerosol.

Pharmacotechnological advantages include: high fine particle fraction in the soft mist generation process, with great amount of respirable particles (the majority of particles being >1 μm to avoid loss during exhalation and systemic absorption, and <5,8 μm to avoid oropharyngeal deposition), ensuring a high lung deposition in the central, intermediate and peripheral regions; unique, slow-moving, long-lasting aerosol characteristics which simplifies co-ordination of activation with inspiration (easy to inhale technique with an increased window of opportunity between actuation and inhalation); dose reproducibility with spray volume uniformity; active substance protection in moisture-insensitive device cartridge, with no microbiological contamination of the unaerosolized solution; no risk of erroneous use of the device after the specified number of actuations due to automatically locking mechanism; no harmful propellants for the pacients or for the environment, and no external power source required (eco-friendly device). Other favourable characteristics of Respimat® SMI include good usability (easy and convenient to use, not dependant on inspiratory flow rate, intuitive design that encourages correct use, uncomplicated learning to use, safe device handling with low risk of unintentional misuse, incorporated dose indicator for an easy feedback to the patient about the remaining doses and reminder to refill the prescription in time), once-daily dosing with improved adherence to treatment, multiple-dose device ensuring a monthly drug supply, and device design **preference features** (pocket sized, portability and easy to carry, comfortable mouthpiece with attached cap to avoid accidental loss, durability, hygienic, accepted design)[13-17].

There are **pharmacoeducational** opportunities of Respimat® SMI use, patients being informed about an easy mnemonic for daily dosing (turn, open, press). Moreover, the preparing of Respimat® SMI for the first-time use is rapid, the priming for the first-time use is not complicated, and the changing of the depleted inhaler poses no problems[1]. The patient **preference and satisfaction** are in favour of Respimat® SMI compared with other inhalers, as evaluated by scores of the willingness to continue using the inhalation device[15,16]. The advantageous cost-effectiveness of tiotropium SMI in asthma was assessed by the pharmacoeconomic impact of add-on treatment with tiotropium Respimat® in patients with uncontrolled asthma despite ICS/LABA treatment, using a Markov stochastic model of probability, taking into account the levels of asthma control and exacerbatioons, and analysing QALY (Quality-adjusted life-year)[18].

In conclusion, in a bief pharmacological rationale for tiotropium Respimat® in asthma, this drug is an efficacious inhaled long-acting anticholinergic, with complex mechanisms of action, delivered *via* an unique soft mist™ inhaler. This innovative device, with a special uniblock system, emitting multidoses for a monthly supply of drug, was recently approved in adult asthma for the once-daily inhaled delivery of tiotropium bromide. ■

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