



TIOTROPIUM

Introduction

Tiotropium (trade name in Australia, “**Spiriva**”) is a **long acting** synthetic inhalational anticholinergic agent.

It is used as preventive treatment for patients with COPD and asthma.

Long-acting anticholinergics inhalant agents should not be used for immediate relief of bronchospasm symptoms.

History

Tiotropium was developed in 1991 and became available for clinical use in 2004, under the trade name of “**Spiriva**”.

Chemistry

Tiotropium bromide is a quaternary ammonium compound.

Classification

The inhalational anticholinergic agents can be classified thus:

1. **Short-acting anticholinergic inhalational agents:**
 - Ipratropium
2. **Long-acting anticholinergic inhalational agents:**
 - Aclidinium
 - Glycopyrronium
 - **Tiotropium**
 - Umeclidinium

Preparations

Tiotropium bromide as:

DPI:

- 18 mcg (capsules)

Inhaler:

- 2.5 mcg/dose

Mechanism of Action

Tiotropium is a long acting, specific antimuscarinic (anticholinergic) agent.

It has similar affinity to the muscarinic receptor subtypes M1 to M5.

In the airways, tiotropium acts on M3-receptors on smooth muscle to cause bronchodilation.

The long duration of effect of tiotropium is likely to be due to its slow dissociation from M₃ receptors, (significantly longer than ipratropium).

Pharmacodynamics

The bronchodilation following inhalation of tiotropium is primarily a local effect on the airways, not a systemic one.

Bronchodilation lasts at least 24 hours.

Pharmacokinetics

Absorption:

- Tiotropium is administered by inhalation.

Approximately 40 % of the inhaled dose of tiotropium is deposited in the lungs, the target organ, the remaining amount is deposited in the gastrointestinal tract

Tiotropium is poorly absorbed from the gastrointestinal tract. Bioavailability is only 2-3 % for oral solutions.

Distribution

- Plasma protein is 72 %
- Volume of distribution is 32 L/kg.

Metabolism and excretion:

- Tiotropium is predominantly renally excreted unchanged.

- The effective half-life of tiotropium ranges between 27 - 45 hours following inhalation by patients with COPD or asthma.

Indications

These include

1. COPD:
 - Long-term maintenance treatment of bronchospasm and dyspnoea in patients with COPD.
 - Prevention of COPD exacerbations.

Note that ipratropium should be stopped if treatment with a **long-acting anticholinergic** is required for COPD

2. **Maintenance** treatment of asthma in patients receiving an **inhaled corticosteroid** (high dose) and a **long-acting beta-2 agonist**

Contra-indications/precautions

These include:

1. Known hypersensitivity to atropine or its derivatives or to any excipients of its preparations.
2. Like other drugs with anticholinergic activity, tiotropium bromide should be avoided or used with caution in patients in whom atropine-like effects may precipitate or exacerbate a pre-existing clinical condition.

Patients at risk include those with narrow acute angle closure glaucoma, urinary retention or constipation.

3. Avoid powder or mist contact with the eyes
4. Tiotropium is predominantly renally cleared; patients with CrCl <50 mL/minute may be at increased risk of anticholinergic adverse effects.

Pregnancy

Tiotropium is a category B1 drug with respect to pregnancy.

Category B1 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been

observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Ipratropium is the preferred anticholinergic bronchodilator in pregnancy. However, if the patient has been stable on tiotropium prior to conception, or if it is considered the medicine of choice, then it is reasonable to consider the use of tiotropium during pregnancy.⁴

Breast feeding

Inhaled tiotropium is considered safe to use during breastfeeding due to the low oral bioavailability and maternal serum levels after use.

However, monitor the infant for signs of anticholinergic adverse effects such as a dry mouth, urinary retention, constipation and an increased heart rate.

Adverse Effects

Adverse effects are usually not severe.

They may include

1. Dry mouth, throat irritation
2. Tachycardia
3. Hypersensitivity reactions.
4. Blurred vision / acute angle-closure crisis.
5. Urinary retention
6. Constipation.

Dosing

Long-acting anticholinergics inhalant agents should not be used for immediate relief of bronchospasm symptoms.

COPD: DPI 1 capsule (18 micrograms) inhaled once daily.

Asthma, COPD: Age > 18 years, 2 inhalations (5 micrograms) once daily.

References

1. eTG - November 2015.
2. Tiotropium in Australian Medicines Handbook Website, Accessed July 2016.
3. Tiotropium in MIMs Website, 1 September 2015.
4. RWH Pregnancy and Breastfeeding Guidelines, 18 May 2016.

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