drug information perspectives

Volume 27 (4) 2007

Contents
Tiotropium
Kathy McInnes B.Sc.(Pharm.)

TIOTROPIUM

SYNONYM: Ba679BR

TRADE NAME: Spiriva

CLASSIFICATION: Muscarinic receptor antagonist; quaternary ammonium compound; anticholinergic bronchodilator

ACTION: Muscarinic receptor antagonist. Reduces cholinergically-mediated bronchoconstriction by binding to muscarinic receptors in the lung. Nonselective; binds to M1, M2 and M3 receptors. Quickly dissociates from M2 receptors. Prolonged effect is due to slow dissociation from M1 and M3 receptors, with a half-life of 35 hours on the human M3 receptor. Structurally similar to ipratropium and atropine.

PHARMACOKINETICS:
- ***Half-life***: 5-6 days
- ***Absorption***: An estimated 20% of an inhaled dose reaches the lungs, where it is rapidly and well absorbed, attaining peak plasma concentration in 5 minutes with an absolute bioavailability of 19.5%. The remaining 80% of a dose is deposited in the GI tract from which, due to the quaternary ammonium structure, little is absorbed, with an oral bioavailability of 2-3%.
- ***Distribution***: 75% plasma protein bound. Does not cross the blood brain barrier because of the quaternary ammonium structure.
- ***Metabolism***: 20-30% of absorbed drug is metabolized. This involves nonenzymatic cleavage to inactive metabolites and P450 enzymes CYP 2D6 and 3A4.
- ***Elimination***: Of the total dose, 14% is eliminated in urine, the remainder in feces as non-absorbed drug.
- ***Special populations***:
  - ***Elderly***: Reduced clearance.
  - ***Renal impairment***: In patients with moderate or severe impairment, plasma levels and bioavailability increase.

B.C. Drug and Poison Information Centre
1081 Burrard Street, Vancouver, B.C. V6Z 1Y6
Phone: (604) 682-2344; Ext: 62126 Fax: (604) 806-8262

USES AND EFFICACY:

Uses: Maintenance treatment of **chronic obstructive pulmonary disease (COPD)**. Regular use improves trough FEV1 by 12% over baseline, improves morning and evening PEFR, reduces lung hyperinflation, reduces the symptoms of wheezing and shortness of breath, reduces the use of rescue medication, and reduces the frequency of exacerbations and hospitalization. It is not a rescue medication for treatment of acute episodes of bronchospasm.

Major clinical trials

One-year trial (2002): In a randomized, double-blind, placebo-controlled study of 921 patients with COPD (baseline FEV1 39% predicted), after one year both trough FEV1 and FVC increased up to 13% over baseline. Both morning and evening PEFR increased. Therapy reduced the symptoms of wheeze and shortness of breath, but not cough or chest tightness. COPD exacerbations were reduced from 0.95 to 0.76 events per patient-year, and exacerbation-associated hospitalizations were reduced by 47% from 0.161 to 0.086 events per patient-year. Study limitations: 24% of patients discontinued the trial early due to drug expiration, which could bias the results in favour of drug treatment in a progressive disease such as COPD (Eur Respir J 2002;19:217-24.).

Versus ipratropium (2002): A randomized, double-blind trial compared the effects of tiotropium once daily versus ipratropium four times daily in 535 patients with COPD (baseline FEV1 40-42% predicted). After one year, more patients taking tiotropium had a clinically significant improvement of 1 unit change in dyspnea (31% versus 18%, NNT=8 for a 1 unit change versus ipratropium). More patients taking tiotropium achieved a clinically significant improvement in quality of life (52% versus 35%, NNT=6 versus ipratropium). One or more exacerbations occurred in fewer patients taking tiotropium over the course of the year (35% versus 46%). There was no significant difference in hospitalizations due to exacerbations (Eur Respir J 2002;19:209-216).

Clinical course: A single dose improves FEV1 in 15 minutes, with peak effect in 2-4 hours, and lasts up to 32 hours with some residual effect at 72 hours. Chronic dosing improves trough FEV1 in one week and this response is maintained. Discontinuation returns FEV1 to baseline but there is no rebound deterioration.

Place in therapy

Tiotropium is a long-acting bronchodilator that reduces the symptoms of COPD when inhaled once daily. It is a first-line choice for maintenance treatment of COPD.

Advantages

- Once daily dosing
- Proven benefit in COPD

Disadvantages

- Provides symptomatic relief but does not alter the natural history of COPD.
- Dry mouth is more common with tiotropium than with ipratropium (12% versus 6%).

Comparisons:

Versus ipratropium: Tiotropium is more effective than ipratropium at reducing the need for rescue bronchodilators, improving dyspnea and quality of life, and reducing exacerbations. It has not been shown to be superior at reducing exacerbation-related hospitalizations, although events were numerically fewer with tiotropium. Dry mouth is more common with tiotropium than with ipratropium (12% versus 6%).

Versus long-acting beta agonists: Tiotropium is similar or more effective at improving quality of life and dyspnea and reducing exacerbations. It has not been superior at reducing hospitalizations, although events were numerically fewer with tiotropium.

Investigational/unapproved uses

Asthma: M2 receptors (autoreceptors that impair acetylcholine release) are impaired in asthma, leading to a dominance of M1- and M3-induced bronchoconstriction, especially at night. Antagonism by tiotropium of M1 and M3 receptors, with only a short antagonism of M2 receptors, may be beneficial, but there are no published reports.

Combination therapy in COPD: Untested but theoretically beneficial effects of combination tiotropium and long-acting beta agonist or corticosteroid drugs.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications

- **Hypersensitivity** to tiotropium or related drugs (atropine, ipratropium).
- **Hypersensitivity to lactos**e (powder contains lactose).
- This product is **NOT indicated for immediate treatment of acute bronchospasm** as rescue therapy.
- **Do not swallow** (for inhalation only).

Precautions

- **Narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction** (may worsen symptoms due to anticholinergic effects).
- **Elderly**: Higher risk of dry mouth, constipation (decreased renal clearance with age).
- **Children** (no data).
- **Renal impairment** (excreted renally; monitor).

PREGNANCY AND LACTATION:

Pregnancy: Not teratogenic in animals. Rats given 35 times the recommended human daily dose by inhalation displayed fetal resorption, loss of litters, reduced number of live pups, reduced pup weight, and delayed sexual maturation. No data in humans. Use only if benefit outweighs risk.

Lactation: Rodent studies show excretion into milk. No data in humans. While the manufacturer indicates that the drug should only be used if expected benefit outweighs any risk to the infant, the likelihood of toxicity is theoretically reduced by the low oral bioavailability of tiotropium (see PHARMACOKINETICS).

SIDE EFFECTS

Most undesirable effects are typical anticholinergic effects.

Cardiovascular: Usually no change in vital signs. Angina pectoris (1-3%); atrial fibrillation, supraventricular tachycardia (< 1%); arrhythmias including atrial flutter, AV block, increased QT interval, torsades, ventricular fibrillation, death (case reports).

CNS: Depression (1-3%, rate exceeded that in placebo group).

Dermatologic: Rash, tongue edema, lip swelling, angioedema (case reports).

Endocrine/Metabolic: Hypercholesterolemia, hyperglycemia (1-3%).

Gastrointestinal: Dry mouth (the most common adverse event; 8-13% more than in placebo group ($p<0.05$); more common than with ipratropium (12-15% versus 6-10%); onset in 4 weeks, usually mild and resolves, or may persist in 2/3 of patients). Constipation (4% versus placebo 2%); bowel obstruction (one case); gastroesophageal reflux (1-3%); absent taste, pancreatitis, mouth irritation (case reports).

Genitourinary: Difficulty urinating and urinary retention (<1%).

Neuromuscular: Arthritis (at least 3%); skeletal pain (1-3%); leg pain (1-3%).

Ocular: Cataract (1-3%); blurred vision, acute angle closure glaucoma (case reports).

Respiratory: Cough (at least 3%); laryngitis (1-3%). Oropharyngeal irritation, paradoxical bronchospasm, cough, throat irritation, hoarseness, dyspnea, bronchospasm (case reports).

Other: Lack of efficacy (multiple case reports); disease exacerbation, decreased therapeutic response (multiple case reports).

INTERACTIONS

Partial metabolism by CYP2D6 and 3A4 suggests that inhibitors of these enzymes could increase tiotropium levels, but low oral bioavailability reduces this risk (see PHARMACOKINETICS).

DRUG	EFFECT	MECHANISM	IMPORTANCE
Anticholinergic drugs	Increased anticholinergic side effects	Additive	Caution

DOSAGE:

Adults:
Chronic obstructive pulmonary disease: Inhalation: 18 mcg once daily at the same time each day. Increasing the dose does not increase benefit.

Elderly: No dosage adjustment required (see Renal Impairment).

Children: No data.

Hepatic impairment: No dosage adjustment required.

Renal impairment: No dosage adjustment required, but careful assessment and monitoring is recommended in patients with decreased renal function (creatinine clearance less than or equal to 50 mL/minute). Use in these patients only if benefits outweigh the risks.

NURSING IMPLICATIONS
This medication is not for immediate treatment of bronchospasm. It is not a rescue medication. If bronchospasm occurs, the patient will require a fast-acting relief medication.

This medication has a similar action to ipratropium (Atrovent). These two drugs should not be taken together. If the patient has been taking ipratropium before, discontinue ipratropium when starting tiotropium.

For the administration technique involved with use of the HandiHaler, see PATIENT INSTRUCTIONS or the package insert. Monitor the patient's inhalation technique; if it is not correct, give instruction or refer to the physician or pharmacist for instruction.

It is important to remove the foil backing from only one capsule at a time as effectiveness may be reduced if a capsule is exposed to air for a longer period of time.

This medication contains lactose as a carrier. It should not be used in patients with a hypersensitivity to lactose.

The most common side effect is dry mouth. This may be alleviated by rinsing the mouth, sucking on a hard sugarless candy or by chewing sugarless gum. Other side effects include constipation, increased heart rate, blurred vision, atrial fibrillation, supraventricular tachycardia, and urinary retention. If these or other symptoms occur, contact the physician.

Store capsules and HandiHaler device at room temperature. Protect from moisture. Do not freeze.

PATIENT INSTRUCTIONS
Tiotropium (tee-oh-TRO-pee-um) is used as regular maintenance therapy in patients with chronic obstructive pulmonary disease. It helps to open up the air passages to the lungs and makes breathing easier. It can keep your airways open for 24 hours.

Take this medication exactly as directed by your physician. Do not take more than is prescribed.

This medication does not act fast enough to give immediate relief of acute episodes of bronchospasm. Use the "relief medication" your physician has prescribed for a rapid effect.

This medication has a similar action to ipratropium (Atrovent). These two drugs should not be taken together. If you have been taking ipratropium before, stop taking ipratropium when starting tiotropium.

Ask your pharmacist for written illustrated instructions on how to use your inhalation device properly.

Before taking this medication for the first time, ensure that your physician is aware if you have any of the following conditions: kidney problems, difficult urination, glaucoma, enlarged prostate, bladder neck obstruction, pregnancy, breast-feeding, or a history of allergy to tiotropium, ipratropium or atropine. This medication contains lactose. Do not use the medication if you have a hypersensitivity to lactose.

Do not swallow the capsules.

Use the medication at the same time each day.

This medication should only be used with the HandiHaler device. Do not use other capsules in the HandiHaler device.

The blister card contains two strips joined together by a perforated line. Before taking the first capsule from the blister card, separate the blister strips by tearing along the perforation.

Do not open the foil until ready to use the capsule. After using the first capsule from a package, the remaining four should be used over the next four consecutive days.

To use the HandiHaler device:
a. Open the dust cap by pulling it upwards.
b. Open the mouthpiece.
c. Peel the aluminum foil from the back of the blister strip until one capsule is fully visible. If more than one capsule is exposed, discard the exposed unused capsule. Do not store the capsule in the HandiHaler device. The drug should be used as soon as it is exposed in the blister pack, or else its effectiveness may be reduced.
d. Remove one capsule and place it in the centre chamber of the HandiHaler device. It does not matter which end of the capsule is put into the chamber.
e. Close the mouthpiece (you hear a click). Leave the dust cap open.
f. Hold the HandiHaler with the mouthpiece pointing upwards. Press the green button fully in once, then release. This makes holes in the capsule to allow the medication to reach you.
g. If your chest is congested with mucous, cough to clear your lungs before you inhale the contents of the capsule. Breathe out completely without the Handihaler. Do NOT breathe into the mouthpiece at any time.
h. Put the HandiHaler to your mouth and close your lips tightly around the mouthpiece. Keep your head upright and breathe in slowly and deeply. You should hear the capsule vibrate. Breathe in until your lungs are full. Hold your breath for as long as is comfortable (try to count to ten). Remove the HandiHaler from your mouth. Breathe out slowly. Resume breathing normally.
i. To ensure the contents of the capsule are inhaled, repeat steps g and h once more.
j. When you have finished breathing in the powder, open the mouthpiece. Tip out the used capsule into the garbage. There may be a small amount of powder left in the capsule. This is normal. Do not touch the used capsule with your hands. If you get dry powder on your hands, wash them thoroughly.
k. Close both the mouthpiece and the dust cap for storage of the HandiHaler device.

Do not let the powder enter your eyes since this may cause your vision to blur and your pupils to dilate (get larger).

The HandiHaler device should be cleaned once a month. See package insert for directions.

This medication can cause dry mouth or bad taste. Rinsing your mouth may help, or try sucking on a hard sugarless candy or chewing sugarless gum. If any unusual effects occur, including an increase in breathing problems, swelling of the lips or face, or problems with urination, vision or constipation, notify your physician.

If you have experienced any unexpected or serious reactions to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

Store this medication in a cool dry place at room temperature, away from heat, light and moisture, and out of the reach of children.

PRESENTATION:
Capsule for inhalation: 18 mcg dry powder per capsule with lactose as the carrier (equivalent to 22.5 mcg tiotropium bromide monohydrate). Capsule is to be used for inhalation only via the breath-actuated HandiHaler device.
Available as blister card containing two 5 cavity strips joined by a perforated line in cartons of 30 or 60 capsules.

References are available on request.