drug information perspectives

Volume 30 (2) 2010

Contents

TROSPIUM

TRADE NAMES: Sanctura XR, Trosec

CLASSIFICATION:
Anticholinergic; muscarinic receptor antagonist ; antispasmodic; quaternary ammonium

ACTION

- Muscarinic receptor antagonist. Blocks the effects of acetylcholine on muscarinic receptors.
- Equally selective for M1, M2, M3, M4 and M5 muscarinic receptors. Little effect on nicotinic receptors.
- Inhibits contractions of bladder detrusor muscle, increases bladder capacity, and increases urine volume at first contraction, thus potentially reducing urinary urge and incontinence.
- Toxicity potential: Trospium is a quaternary ammonium compound that is ionized at physiological pH, with a resultant low ability to cross cell membranes including the blood brain barrier, suggesting a low potential for anticholinergic-related cognition deficits.
- Increases heart rate via M2 stimulation on sinus node cells.
- There are 5 muscarinic receptor subtypes, M1-M5. Tissues generally contain more than one subtype: brain (mostly M1 but also M3 and M4); salivary glands (M1 stimulation produces lubricating secretions while both M1 and M3 stimulation produce low viscosity secretions); heart (mostly M2 but also M3); eye ciliary muscle (M3 and M5); bladder (most detrusor muscle contraction is due to M3 stimulation, while more abundant M2 stimulation reduces inhibition of contraction); gastrointestinal tract (M2 and M3); gastric acid secretion (M1).

PHARMACOKINETICS
Half-life:

- Regular release tablet: 18 hours
- Extended release capsule: 36 hours

Absorption: Regular release tablet: Slowly and poorly absorbed, mostly in the upper small intestine, possibly related to its quaternary ammonium structure resulting in a positive charge and low lipophilicity; as well, secretion from blood into the gut lumen by P-glycoprotein has been indicated in rats. Bioavailability 3-10% and shows a large degree of variability (3-16%) including intra-individual variability of 20%. Administration with a high-fat meal

reduces drug absorption by 35% (capsules) to 70-80% (tablets). Peak drug level at 4.5 (tablet) to 5 hours (capsules) is lower for the capsules than the tablets. Absorption is 33% lower if taken in the evening rather than in the morning.
Distribution: Plasma protein bound 50-85%. Widely distributed. Because it is a quaternary ammonium compound, in theory it should not cross the blood brain barrier easily and this has been demonstrated in rats.
Metabolism: By esterases. Less than 5% of renal metabolites are produced by P450 enzymes. No active metabolites are expected.
Elimination: Most of a dose is not absorbed, thus fecal elimination is high (85%). Most of the approximately 10% of a dose that is absorbed is eliminated in the urine (70%), and some in the feces (20%). Urinary elimination involves active renal tubular secretion and glomerular filtration (40% as metabolites, 60% as unchanged drug).
Special populations:

- **Elderly**: No change; conflicting data.
- **Hepatic impairment**: Mild hepatic impairment (Child-Pugh class A): Cmax increased 12%. Moderate or severe hepatic impairment (Child-Pugh class B or C): Cmax increased 63%; renal clearance increased 51%, possibly due to renal compensation.
- **Renal impairment**: Mild or moderate impairment: No data. Severe renal impairment: Regular release tablets: increased AUC 45% and increased Cmax 2-fold.
- **Sex difference**: Conflicting data; possibly increased Cmax, AUC and half-life in females.
- **Race**: No data.
- **Pharmacogenetics**: Not applicable.

USES AND EFFICACY

***Uses*: Symptomatic treatment of overactive bladder.**
Compared with placebo, it reduces the urge to void by about 1 urge/day as well as reducing urge severity, reduces the number of episodes of incontinence by 14-20%, and slightly reduces the number of voids by about 1/day. There is a strong placebo response. Effects are consistent with documented improvements in quality of life. Nocturnal wakening to void has also improved, and the average volume of urine per void increases, although only by 14-26mL. Response rate: Approximately 71% of patients can achieve a 50% or greater decrease in incontinence episodes, compared with 54% of patients taking placebo. A normal pattern of urination with no incontinence is achieved by 21% of patients versus 11% who take a placebo.

Clinical course: Benefit is detectable in the first week of therapy, possibly within 3 days, with further improvement over the first 6 months of therapy.

Major clinical trials
Trospium Study Group 2004: A randomized, double-blind, placebo-controlled trial in 523 patients with overactive bladder (baseline average 13 voids/day, 4 urinary incontinence episodes/day, and 2 nocturnal voids/day) evaluated the benefit of 20mg twice daily immediate release trospium. After 12 weeks, in patients given trospium the number of voids/day decreased by 2.37, the number of urinary incontinence episodes decreased by 59%, the number of urges to void decreased by 2.3/day, nocturnal voids decreased by 0.47, and quality of life improved. Patients given placebo also improved, but not as much, with the number of voids/day decreased by 1.29, the number of urinary incontinence episodes decreased by 44%, the number of urges to void decreased by 1.08/day, nocturnal voids decreased by 0.29, and quality of life improved. With trospium 21% of patients became completely dry compared with 11% on placebo. [J Urology 2004;171:2311-2315.] *Study limitations*: Funded by the manufacturer. The placebo response was large.

Long-term comparison with oxybutynin 2003: A randomized, double-blind study of 358 patients with detrusor instability (baseline average 11-12 voids/day, 1.5-2 urinary incontinence episodes/day) compared 52 weeks of treatment with trospium 20mg twice daily versus oxybutynin 5mg twice daily. The two medications had similar efficacy, increasing the maximum bladder capacity and the volume at first unstable contraction, and reducing the frequency of voiding and incontinence. For trospium, progressive improvement was noted in voiding frequency, which decreased from 11.4/day by 1.2 voids/day at 2 weeks, by 2.9 voids/day at 26 weeks, and by 3.5 voids/day by 52 weeks. Urinary incontinence episodes decreased by 1 episode/day for both drugs. Dry mouth was less common with trospium (33% of patients versus 50%). [World J Urol 2003;20:392-399.]

Comparisons
Vs. oxybutynin

- Similar in efficacy, but dry mouth is less common with trospium, and possibly less severe.

Advantages:

- Few drug interactions since it has little involvement with the P450 system.
- A lack of CNS adverse effects, possibly because its chemical structure limits its ability to cross the blood brain barrier, making it well-tolerated and safer, especially in the elderly.
- Dry mouth, a common concern with anticholinergic drugs, appears to be less common with the extended-release once daily dosage form of trospium compared with immediate release trospium and other drugs of this type.

Disadvantages:

- Must be given on an empty stomach for adequate absorption.

Place in therapy:

- Modestly reduces incontinence and the frequent urge to void in patients with overactive bladder, with efficacy similar to other drugs in this class such as oxybutynin and tolterodine. A normal urination pattern is achieved in only about 20% of patients (10% more than with placebo).
- Trospium is a good choice because of its low rate of drug-drug interactions and CNS adverse effects, and the availability of a convenient once daily dosage form that is associated with a low rate of mouth dryness. Quality of life is improved.
- Direct comparisons with other drugs have not been adequately conducted.
- There is a strong placebo response, and there is evidence that behavioural training is as effective as, or more effective than, drug therapy. A trial of bladder training with encouragement should be attempted prior to initiating drug therapy with its potential side effects of dry mouth and constipation.

Investigational/Unapproved Uses:

- ***Detrusor hyper-reflexia in patients with spinal cord injuries***: Decreases detrusor pressure and increases bladder capacity with improvement in symptoms.

CONTRAINDICATIONS AND PRECAUTIONS
Contraindications:

- ***Hypersensitivity***
- ***Urinary retention*** (may cause acute urinary retention)
- ***Gastric retention*** (may reduce gastric motility)
- ***Uncontrolled narrow-angle glaucoma***
- ***Severe renal impairment*** (the extended release capsule is contraindicated because of lack of data and renal elimination; reduce dose of regular release tablet)

Precautions:

- Patients with **bladder outflow obstruction** (risk of developing urinary retention)
- Patients with **decreased gastrointestinal motility or gastrointestinal obstructive disorders** such as pyloric stenosis, myasthenia gravis, severe constipation, ulcerative colitis, gastroesophageal reflux (risk of decreased gastric motility)
- Patients with **controlled narrow angle glaucoma**
- Not evaluated in patients with **CHF, myocardial infarction, hypokalemia** (concern over T wave inversion)
- **Liver impairment** (caution, see Pharmacokinetics); no data on effects in severe liver impairment
- **Elderly** (increased anticholinergic adverse effects of constipation, dry mouth, stomach upset, urinary tract infection and urinary retention)
- **Mild-moderate renal impairment** (renal elimination is a major pathway, caution)
- **Xerostomia, Sjogren's Syndrome** (risk of dry mouth)

- **Report** unexpected or serious reactions to Canada Vigilance, Canada's adverse drug reaction monitoring program.

PREGNANCY AND LACTATION

- In rats given 10 times the expected clinical exposure, maternal toxicity and decreased fetal survival have been documented. No teratogenicity has been reported. No data in humans. Present as a charged quaternary ammonium molecule that may have limited ability to cross the placenta. Consider risk:benefit.
- No data on presence in breast milk in humans. The charged quaternary ammonium molecule is hydrophilic and may have low presence in milk, theoretically. Possible anticholinergic adverse effects in the breast-feeding infant; caution.

SIDE EFFECTS

Well tolerated. The most common effects are dry mouth and constipation, due to anticholinergic effects, with onset in the first month, and possibly in the first week.

Cardiovascular:

- No increase in QT but causes nonspecific, asymptomatic T wave inversions; clinical significance unknown.
- Increased heart rate 3-9bpm.
- Tachycardia (rare).
- No change in blood pressure even at high doses.

CNS:

- Headache (up to 6.5% with the immediate release tablets versus placebo 2-4.6%).
- No sedation or daytime sleepiness even in patients over 75 years of age or at high doses.
- Dizziness (rare).

Gastrointestinal:

- Dry mouth (14-22% with regular release tablets versus placebo 5-8%; 9-13% with extended release capsules versus placebo 3-5%; may improve with time; dose-dependent).
- Constipation (9-10% versus placebo 2-5% for either capsules or tablets; may improve with time).
- Nausea (1.4% with the extended release capsules versus placebo 0.3%).
- Abdominal pain (3.1% with regular release tablets versus placebo 1.1%; 1.4% with the extended release capsules versus placebo 0.3%).
- Dyspepsia (1.2% versus placebo 0.3-0.7%).
- Flatulence (1.2-1.6% vs. placebo 0.5-0.8%).
- Abdominal distension (1% with extended release capsules versus placebo 0.3%).

Genitourinary:

- Urinary retention (1.2% versus placebo 0.3%).
- Urinary tract infection (up to 7% with extended release capsules versus up to 5% with placebo).

Respiratory:

- Nasopharyngitis (3% with extended release capsules versus placebo 2%).
- Cough (2.4% with regular release tablets versus placebo 0.3%).

Other:

- Dry eyes (1.2-1.6% versus placebo 0.2-0.3%).
- Blurred vision (rare).
- Dry skin (rare).
- Nasal dryness (1% with extended release capsules versus placebo 0%).
- Falls in the elderly (1 case).

INTERACTIONS
Does not inhibit the major P450 enzymes *in vitro*.

DRUG	EFFECT	MECHANISM	IMPORTANCE
Acetylcholinesterase inhibitors (donepezil, rivastigmine)	Decreased efficacy of both drugs	Antagonism	Caution
Alcohol	Sedation	Additive	Avoid alcohol within 2 hours of administering the extended- release capsule
Anticholinergic drugs	Increased anticholinergic adverse effects	Additive	Caution
Drugs actively secreted by the kidneys*	Increased levels of either drug	Competition for renal tubular secretion	Caution (theoretical)

*Drugs that are actively eliminated by renal tubular secretion include: digoxin, metformin, morphine, pancuronium, procainamide, tenofovir and vancomycin.

DOSAGE
Guidelines
- Administered at least one hour before meals or on an empty stomach.
- Morning dosing increases the amount of drug absorbed.

Adults:
- Regular release tablets: 20mg twice daily.
- Extended release capsules: 60mg once daily in the morning.

Children: Not approved for use in children. Investigationally, doses of 10-20 mg per day given in two divided doses have been effective and well tolerated in children age 5-13 years with detrusor instability.

Elderly:
Reduce dose of the regular release tablet to 20mg once daily if 75 years of age or older, depending on tolerance. The risk of adverse reactions is increased.

Hepatic impairment:
Caution in moderate or severe impairment; drug levels may be increased (see PHARMACOKINETICS).

Renal impairment:
Mild or moderate renal impairment: No data. Severe renal impairment (ClCr 0.25-0.5mL/sec (15-30mL/minute)): 20mg of the regular release tablet once daily at bedtime. The extended release capsule is contraindicated in severe renal impairment.

NURSING IMPLICATIONS
Trospium is given with water at least one hour before meals or when the patient has an empty stomach, since food reduces its absorption into the body. The extended release capsules are given once daily in the morning with water, at least one hour before a meal.

Extended-release capsules must be swallowed whole. They should not be chewed, crushed or broken.

Monitor urine output. If urinary retention or skin rash occur, stop giving the drug. Notify physician immediately.

The elderly may be especially sensitive to the anticholinergic side effects: severe dry mouth, blurred vision, drowsiness, constipation, urinary retention.

Supervise ambulation. Encourage fluids and dietary fibre intake. Dry mouth may be relieved by sucking on ice chips or by chewing sugarless gum.

Clinical monitoring parameters: improvement in urinary frequency, urgency, nocturia, and urge incontinence. Some improvement is possible in the first week, while maximum benefit may take months of therapy.

Store at room temperature, away from light, and out of the reach of children.

PATIENT INSTRUCTIONS
Trospium (TROSE-pee-um) is used to control the symptoms of an overactive bladder. Symptoms can include the frequent need to urinate or the inability to control urination.

Before taking this medication for the first time, be sure that your physician is aware if you have any of the following conditions: liver impairment, narrow angle glaucoma, urinary outflow problems, kidney disease, gastrointestinal problems such as constipation or gastric obstruction; Sjogren's syndrome.

Take this medication exactly as prescribed. Taking it at the same time each day will help you to remember. For the full effect, it is important to take it on an empty stomach; therefore, take it with water at least one hour before a meal.

If you forget to take a dose, take it before the next meal unless it is almost time for the next dose. Do not take a double dose to make up for a missed dose.

If you are taking an extended release capsule: Swallow each capsule whole, do not crush or chew it.

Some improvement is possible in the first week, while maximum benefit may take months of therapy.

Tell your physician or pharmacist if you are taking any prescription medications or over-the-counter medications. Trospium can interact with various medications.

If you are pregnant or breast-feeding, discuss the use of this medication with your physician.

Some patients may experience dizziness or vision problems. Do not drive a car, operate dangerous machinery, or drink alcohol, until you know how this medication affects you. It has been recommended that you avoid alcohol for two hours before and after taking the extended release capsule, to avoid becoming too drowsy.

This medication may cause you to have a dry mouth. Sucking on ice chips or chewing sugarless gum may help.

This medication may cause constipation. Fluid and dietary fibre intake may help prevent the constipation. Check with your physician if this persists or is bothersome.

Other common side effects that can be seen with trospium include headache, abdominal pain and dry eyes. Check with your physician if these side effects persist or are bothersome.

If you develop difficulty urinating, stop taking this product and contact your physician as soon as possible.

In a hot environment, this drug can reduce sweating and increase the risk of heat stroke. Drink plenty of fluids.

If you have experienced an unexpected or serious reaction 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 drug in its original container, away from heat, light and moisture, and out of the reach of children.

PRESENTATION
Tablet: 20mg.
Extended release capsule: 60mg.

References are available on request.

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