ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

The drug in overactive bladder disease: Trospium Chloride

*P.Venkat Rao[1], K.Amrutha[1], K.Padmaja[1], P.L.Suchitra[1], I.Madhuri[1] and T.Prabhakar[2]

[1]Raghu College of Pharmacy,Dakamarri,Visakhapatnam(Dist)-531162
[2]A.U.College of Pharmaceutical Sciences,Andhra University,Visakhapatnam-53003

ABSTRACT

Trospium chloride is a quaternary ammonium compound, which is a competitive antagonist at muscarinic cholinergic receptors. Preclinical studies using porcine and human detrusor muscle strips demonstrated that trospium chloride was many-fold more potent than oxybutynin and tolterodine in inhibiting contractile responses to carbachol and electrical stimulation. The drug is poorly bioavailable orally (< 10%) and food reduces absorption by 70%– 80%.

*Corresponding author

ISSN: 0975-8585

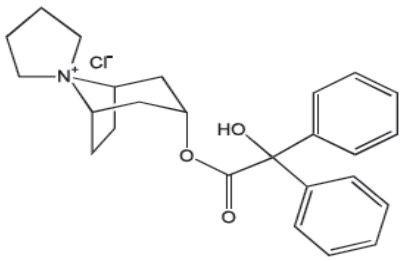
Introduction

Trospium chloride is a quaternary ammonium compound, which is a competitive antagonist at muscarinic cholinergic receptors.

Class: Anticholinergic
Trade Names:Sanctura - Tablets 20 mg
Sanctura XR - Tablets, extended-release 60 mg
Trosec (Canada)

Chemistry [1]

Trospium chloride also known as azonia-3-α-benziloyloxy-8-spiro-1′- pyrrolidinium chloride has the molecular formula $C_{25}H_{30}NO_3Cl$, and a molecular weight of 427.97. Its chemical name is spiro[8-azoniabicyclo[3,2,1]octane-8,1′-pyrrolidinium]-3-[(hydroxydiphenylacetyl)- oxy]chloride(1α,3β,5α)-(9CI). Solubility in water exceeds 50 mg per mL at room temperature while in light mineral oil it is 9.2×10^{-3} mg/mL .Its log partition coefficient between n-octanol and buffer at pH 7.4 is –1.22). Synthesis and pharmacological activity of this compound was first described in 1966.



Chemical Structure of trospium chloride

ISSN: 0975-8585

Physical properties

Appearance: Trospium chloride is a fine, colorless to slightly yellow, crystalline solid.

Solubility: Very soluble in water approximately 1g/2ml, freely soluble in methanol, practically insoluble in methylene chloride.

Dosage forms and strength:

SANCTURA is supplied as 60 mg capsules (white opaque body and orange opaque cap, printed with SAN 60).

Melting point: 266-268°C

Identification tests and limits:

Tests:	Limits:
Identification: I.R. spectrum	
Identification: chloride	
Clarity of 10 % (w/v) aqueous solution:	Clear
Color of 10 % (w/v) aqueous solution:	max. B7
pH of 1 % (w/v) aqueous solution:	5.0 – 7.0
Impurity C (TLC):	max. 0.5 %
Related substances (HPLC):	
Impurity A	max. 0.3 %
Impurity B	max. 0.5 %
Any other impurity:	max. 0.1 %
Total sum of impurities:	max. 1.0 %
Loss on drying (105 °C):	max. 0.5 %
Sulphated ash:	max. 0.1 %
Assay (Argentometry, calculation calculation based on dry substance):	99.0 – 101.0 %
Ethanol (GC):	max. 3000 ppm
Microbiological test:	
Bacteria	max. 1000 cfu/g
Fungi	max. 100 cfu/g
Escherichia coli in 1g	Absent
Salmonella in 10g	Absent
Pseudomonas aeruginosa in 1g	Absent
Staphylococcus aureus in 1g	Absent

ISSN: 0975-8585

Dosage and Administration [2]

Adults : Immediate-release: 20 mg twice daily on an empty stomach or at least 1 h before meals.
Extended-release: 60 mg daily in the morning on an empty stomach, at least 1 h before a meal.

Storage/Stability [7]

Store at controlled room temperature (68° to 77°F)

Pharmacology:

SANCTURA is an antispasmodic, antimuscarinic.

Mechanism of Action

Trospium chloride acts as a direct antagonist at muscarinic acetylcholine receptors in cholinergically innervated organs. It has been shown to have negligible affinity for nicotinic acteylcholine receptors at therapeutic doses, and to not easily cross the blood-brain barrier, yielding a localized, potent anticholinergic for peripheral targets. Its anticholinergic-parasympatholytic action reduces the tonus of smooth muscle in the bladder, effectively reducing the number of required voids, urge incontinence episodes, urge severity and improving retention, facilitating increased volume per void.

Pharmacodynamics

Placebo-controlled studies employing urodynamic variables were conducted in patients with conditions characterized by involuntary detrusor contractions. The results demonstrate that SANCTURA® increases maximum cystometric bladder capacity and volume at first detrusor contraction.

Pharmacokinetics

Absorption: After oral administration, less than 10% of the dose is absorbed. Mean absolute bioavailability of a 20 mg dose is 9.6% (range: 4.0-16.1%). Peak plasma concentrations (Cmax) occur between 5 to 6 hours post-dose. Mean Cmax increases greater than dose-proportionally; a 3-fold and 4-fold increase in Cmax was observed for dose increases from 20 mg to 40 mg and from 20 mg to 60 mg, respectively.

Distribution: Protein binding ranged from 50 to 85% when therapeutic concentration levels (0.5-50 ng/mL) were incubated with human serum in vitro. The ^{3}H-trospium chloride ratio of plasma to whole blood was 1.6:1. This ratio indicates that the majority of ^{3}H-trospium chloride is distributed in plasma. The apparent volume of distribution for a 20 mg oral dose is 395 (± 140) liters.

Metabolism: The metabolic pathway of trospium in humans has not been fully defined. Of the 10% of the dose absorbed, metabolites account for approximately 40% of the excreted dose following oral administration. The major metabolic pathway is hypothesized as ester hydrolysis with subsequent conjugation of benzylic acid to form azoniaspironortropanol with glucuronic acid. Cytochrome P450 is not expected to contribute significantly to the elimination of trospium.

Excretion: The plasma half-life for SANCTURA® following oral administration is approximately 20 hours. After administration of oral ^{14}C-trospium chloride, the majority of the dose (85.2%) was recovered in faeces and a smaller amount (5.8% of the dose) was recovered in urine; 60% of the radioactivity excreted in urine was unchanged trospium.

Contraindications [5]

Patients with or at risk of urinary retention; gastric retention; uncontrolled narrow-angle glaucoma; hypersensitivity to any component of product.

Adverse affects [3]

Gastrointestinal disorders: Dry mouth, constipation, abdominal pain, dyspepsia, flatulence.
Nervous system disorders: Head ache
General disorders: Fatigue
Renal and urinary disorders: Urinary retention
Eye disorders: Dry eyes

Drug interactions [6]

Trospium has the potential for pharmacokinetic interactions with other drugs that are eliminated by active tubular secretion (e.g. procainamide, pancuronium, morphine, vancomycin, metformin, tenofovir, pramlintide, acetyl cholinesterase inhibitors and anticholinergic drugs). Coadministration of Trospium with these drugs may increase the serum concentration of Trospium and/or the coadministered drug due to competition for this elimination pathway.

Precautions [4]

General:

Risk of Urinary Retention: Trospium should be administered with caution to patients significant bladder with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Decreased Gastrointestinal Motility: Trospium should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention. Trospium like other anticholinergic drugs may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony and myasthenia gravis.

Controlled Narrow-angle Glaucoma: In patients being treated for narrow-angle glaucoma, Trospium should only be used if the potential benefits outweigh the risks and in that circumstance only with careful monitoring.

Patients with Renal Insufficiency: Dose modification is recommended in patients with severe renal insufficiency (CLcr < 30 mL/min). In such patients, Trospium should be administered as 20 mg once a day at bed time.

Patients with Hepatic Impairment: Caution should be used when administering Trospium in patients with moderate or severe hepatic dysfunction.

Pregnancy: Teratogenic effects

Pregnancy Category C: Trospium chloride has been shown to cause maternal toxicity in rats and a decrease in fetal survival in rats administered approximately 10 times the expected clinical exposure (AUC). There are no adequate and well controlled studies in pregnant women. Trospium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: Trospium is administered to a nursing woman. Trospium should be used during lactation only if the potential benefit justifies the potential risk to the newborn.

Therapeutic uses:

It is indicated for the treatment of overactive bladder with symptoms of

- Urge urinary incontinence,
- urgency, and
- urinary frequency

REFERENCES

[1] Reuel HP, Murtz G, Boudy S, et al. Arzeimitte forschung 1993; 43: 461.
[2] Cardozo L, Chapple CR, Toozs-Hobson et al. BI Uint 2000;85:659-64.
[3] http://www.drugs.com/mtm/trospium chloride-htm/
[4] http://www.rx list.com/Sanctura drug htm.
[5] http://www.medilexicon.com/drugs/sanctura-php.
[6] http://med guides.medicines.org.UIC/doc.
[7] http://www.drugs bank.com.