ATROVENT® Metered Aerosol (CFC-free)

NAME OF THE MEDICINE

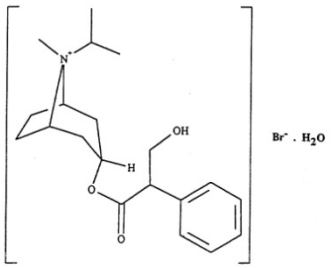
Ipratropium bromide.

The chemical name for ipratropium bromide (as monohydrate) is (1R,3r,5S,8r)-3-[(RS)-(3-hydroxy-2-phenyl-propanoyl)-oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide monohydrate.

The CAS number for ipratropium bromide (as monohydrate) is 66985-17-9.

The molecular formula is $C_{20}H_{30}NO_3Br.H_2O$ and the molecular weight is 430.4.

Ipratropium bromide has the following structural formula:



DESCRIPTION

Ipratropium bromide is a synthetic quaternary ammonium compound, chemically related to atropine. The addition of an N-isopropyl group distinguishes the molecule from atropine and is responsible for a lower lipid solubility.

Ipratropium bromide is a white or off-white crystalline substance. It is freely soluble in methanol, soluble in water and sparingly soluble in ethanol 96%(v/v).

In addition to ipratropium bromide, ATROVENT metered aerosol contains citric acid-anhydrous, water-purified, ethanol-absolute and the non-chlorofluorocarbon (CFC-free) propellant norflurane (also known as HFA [hydrofluoroalkane] 134a).

PHARMACOLOGY

Pharmacotherapeutic group: Anticholinergics
ATC Code: R03BB01

ATROVENT is an anticholinergic bronchodilator. It appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagal nerve. Anticholinergics prevent the increase in intracellular calcium concentration caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Bronchodilation following inhalation of ATROVENT is a local, site specific effect at the bronchial smooth muscle. ATROVENT has no deleterious effect on airway mucous secretion or mucociliary clearance.

The time course of action of ATROVENT also differs from the β_2 agonists in that although the onset of bronchodilator response is seen within 3-5 minutes of administration, peak response is not reached until 1.5-2 hours after inhalation. The duration of significant bronchodilator action is up to 6 hours.

ATROVENT may be used in combination with β_2 agonists. There is evidence that in patients who respond to ATROVENT, the concurrent administration of ATROVENT and β_2 agonists produces a greater relief of bronchospasm than either drug given alone.

Pharmacokinetics

Absorption

Following inhalation, 10 to 30% of the dose (depending on the formulation and inhalation technique) is generally deposited in the lungs. The major part of the dose is swallowed and passes into the gastrointestinal tract. Due to the low gastrointestinal absorption of ipratropium bromide, the bioavailability of the portion of the dose swallowed, accounts for approximately 2% of the dose. This fraction of the dose does not make a relevant contribution to the plasma concentrations of the active ingredient. The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes) and has nearly complete systemic availability.

From renal excretion data (0-24 hours), the total systemic bioavailability (pulmonary and gastrointestinal portions) of inhaled doses of ipratropium bromide was estimated to be in the range 7 to 28%. This is also a valid range for inhalation from ATROVENT CFC-free because the kinetic results (renal excretion, AUC and C_{max}) from the CFC-free and the CFC-containing formulations are approximately comparable.

Distribution

Kinetic parameters describing the disposition of ipratropium bromide were calculated from plasma concentrations after intravenous administration. A rapid biphasic decline in plasma concentrations is observed. The volume of distribution (V_z) is 338 L (approximately 4.6 L/kg). The half-life of the terminal elimination phase is about 1.6 hours. The drug is less than 20% bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier, consistent with the ammonium structure of the molecule.

Metabolism

The mean total clearance of the drug is 2.3 L/min. The major portion, approximately 60% of the systemically available dose, is eliminated by metabolic degradation, probably in the liver. The main urinary metabolites bind poorly to the muscarinic receptor and have no activity.

Elimination

Approximately 40% of the systemically available dose is cleared via urinary excretion, corresponding to an experimental renal clearance of 0.9 L/min. After oral dosing less than 1% of the dose is renally excreted, indicating an insignificant absorption of ipratropium bromide from the gastrointestinal tract.

In excretion balance studies, after intravenous administration of a radioactive dose, less than 10% of the drug-related radioactivity (including parent compound and all metabolites), are excreted via the biliary-faecal route. The dominant excretion of drug-related radioactivity occurs via the kidneys.

CLINICAL TRIALS

The use of ATROVENT metered aerosol, delivered using CFC-containing propellants, is well established in clinical practice. A clinical programme has been conducted to demonstrate the therapeutic equivalence of ATROVENT CFC-free and

CFC-containing metered aerosols. The safety and efficacy of ATROVENT CFC-free metered aerosol, in chronic obstructive pulmonary disease (COPD) and asthma, was established from the results of one 12-month and two 12-week safety and efficacy trials conducted in COPD, a 12-week study in asthmatic adults and a 12-week safety study in asthmatic children.

A randomised, open-label, parallel design 12-month study in COPD patients, compared the safety and efficacy of ATROVENT metered aerosols containing either CFCs (n=151) or norflurane (n=305). Time profiles of forced expiratory volume in one second (FEV_1) mean changes from baseline on all test days demonstrated the efficacy and overall comparability of the ATROVENT CFC-free and CFC-containing aerosols. The two formulations were generally comparable throughout the trial with respect FEV_1 area under the curve for 0 to 6 hours (AUC_{0-6}). The overall safety profile indicated that both treatments were well tolerated.

A 12-week, double-blind, randomised trial in COPD patients, comparing safety and efficacy of ATROVENT CFC-free and CFC-containing metered aerosols (n= 118 and 56 respectively), concluded there were no differences in respect of changes in morning and evening peak expiratory flow rates. In addition, a randomised, double-blind, placebo and active controlled study of 12-weeks duration in COPD patients, concluded that ATROVENT CFC-free 42 μg (n=125) and 84 μg (n=127) were significantly more effective than placebo in terms of adjusted mean FEV_1 AUC_{0-6} and peak response. For each trial, the safety profiles of both formulations were found to be comparable.

A multi-dose comparison of ATROVENT CFC-free with CFC-containing metered aerosol in a 12-week, double-blind, parallel group study of adult patients with bronchial asthma, demonstrated that patients who switched to the CFC-free aerosol (n=159) from the CFC-containing aerosol (n=75), had no change in daily peak expiratory flow rate values and usage of rescue medication. Similar results were observed in paediatric patients with bronchial asthma in a 12-week, double-blind, parallel group study comparing ATROVENT CFC-free (n=133) with the ATROVENT CFC-containing aerosol (n=58). For both studies, the adverse event profile of both formulations was very similar for all events reported.

In summary the data shows that ATROVENT CFC-free metered aerosol is comparable in terms of efficacy and safety to the CFC-containing formulation.

INDICATIONS

ATROVENT metered aerosol is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with asthma and chronic obstructive pulmonary disease (COPD).

CONTRAINDICATIONS

Known hypersensitivity to atropine or its derivatives (such as the active substance iptraropium bromide), or to any of the other ingredients of ATROVENT.

PRECAUTIONS

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of ATROVENT, as demonstrated by rare cases of urticaria, angio-oedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

Paradoxical bronchospasm

As with other inhaled medicines ATROVENT may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs ATROVENT should be discontinued immediately and substituted with an alternative therapy.

Anticholinergic effects

Like other drugs with anticholinergic activity, ipratropium bromide should be avoided or used with caution in patients where atropine-like effects may precipitate or exacerbate a pre-existing clinical condition. Patients at particular risk are those with eyes with narrow iridocorneal angles as acute angle-closure glaucoma may be precipitated, or patients with a tendency towards urinary retention or constipation.

Ocular complications

ATROVENT should be used with caution in patients predisposed to narrow-angle glaucoma.

There have been isolated reports of ocular complications (mydriasis, increased intraocular pressure, acute angle glaucoma, eye pain) as a result of direct eye contact of ipratropium bromide formulations. Thus, patients must be instructed in the correct administration of ATROVENT and warned not to allow the aerosol to enter the eyes.

Patients who may be predisposed to glaucoma should be specifically warned to protect their eyes. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema, may be signs of acute angle-closure glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

Renal and urinary effects

ATROVENT should be used with caution in patients with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-neck obstruction).

Gastro-intestinal motility disturbances

Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances.

Effects on Fertility

Clinical data on fertility are not available for ipratropium bromide.

Use in Pregnancy (Category B1)

Care is recommended during pregnancy, particularly in the first trimester. The safety of ATROVENT during pregnancy has not been established. The benefits of using ATROVENT when pregnancy is confirmed or suspected must be weighed against possible hazards to the foetus. Studies in rats, mice and rabbits showed no embryo-toxic nor teratogenic effects.

Use in Lactation

No specific studies are available to determine the excretion of ipratropium bromide in human breast milk. Although lipid-insoluble quaternary cations pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent,

especially when administered by inhalation. However, as many drugs are excreted into breast milk, caution should be exercised when ATROVENT is administered to breastfeeding mothers.

Genotoxicity

Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Carcinogenicity

Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic potential at dietary doses up to 6 mg/kg/day for ATROVENT.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis and blurred vision during treatment with ATROVENT. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

Propellants

ATROVENT CFC-free metered aerosol contains the hydrofluoroalkane propellant norflurane. In animal studies, norflurane has been shown to have no significant pharmacological effects, except at very high exposure concentrations when narcosis and a relatively weak sensitisation to the arrhythmogenic effects of catecholamines were found. The potency of the cardiac sensation was less than that of trichloromethane.

Excessive inhalation of the aerosol should, however, be avoided as this carries a potential hazard, both from the propellant as well as from overdosage of the active therapeutic agent contained in the formulation. The recommended dose should not be exceeded and the patients should be so informed.

INTERACTIONS WITH OTHER MEDICINES

The chronic co-administration of ATROVENT inhalation with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of ATROVENT with other anticholinergic drugs is not recommended.

Beta-adrenergics and xanthine preparations may intensify the bronchodilatory effect of ATROVENT.

ADVERSE EFFECTS

Many of the listed undesirable effects can be assigned to the anticholinergic properties of ATROVENT. As with all inhalation therapy ATROVENT may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance during post approval use of the drug. The most frequent side effects reported in clinical trials were headache, dizziness, throat irritation, cough, gastrointestinal disorders (including constipation, diarrhoea, gastrointestinal motility disorder, dry mouth nausea, stomatitis, oedema mouth and vomiting).

If the substance enters the eyes by inappropriate handling, mild and reversible disturbance of accommodation may occur. Other ocular complications have also been reported (see **PRECAUTIONS**). However, acute angle-closure glaucoma has been reported following direct eye contact.

Allergic-type reactions such as angio-oedema of the tongue, lips and face may also occur.

The following adverse reactions were reported in the clinical studies at the following frequency: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Immune system disorders

Uncommon: hypersensitivity, anaphylactic reaction

Nervous system disorders

Common: headache, dizziness

Eye disorders

Uncommon: vision blurred, mydriasis, intraocular pressure increased, glaucoma, eye pain, halo vision, conjunctival hyperaemia, corneal oedema,
Rare: accommodation disorder

Cardiac disorders

Uncommon: palpitations, supraventricular tachycardia
Rare: atrial fibrilation, heart rate increased

Respiratory, thoracic and mediastinal disorders

Common: throat irritation, cough
Uncommon: bronchospasm, bronchospasm paradoxical, laryngospasm, pharyngeal oedema, dry throat

Gastrointestinal disorders

Common: dry mouth, nausea, gastrointestinal motility disorder (including reports of change in bowel motions and habits, dyspepsia, gastrointestinal reflux and flatulence)[1]

Uncommon: diarrhoea, constipation, vomiting, stomatitis, oedema mouth

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus, angioedema
Rare: urticaria

Renal and urinary disorders

Uncommon: urinary retention

[1] [1] The definition is based on a post-hoc review of all ADR terms reported in the defined study dataset. Terms that report a clinically related term with greater medical specificity were excluded and added to the more specific term (e.g. “nausea”, “vomiting”).

DOSAGE AND ADMINISTRATION

Note: One puff (metered dose) of ATROVENT contains 21 micrograms of ipratropium bromide [equivalent to 20 micrograms of ipratropium bromide (anhydrous)].

If the response to the treatment is inadequate, medical advice should be sought so that appropriate measures can be taken. It is advisable not to greatly exceed the recommended daily dose as this suggests additional therapeutic modalities may be needed.

If therapy does not produce a significant improvement or if the patient's condition gets worse, medical advice must be sought in order to determine a new plan of treatment. In the case of acute or rapidly worsening dyspnoea, a doctor should be consulted immediately.

Adults

Two puffs 3 to 4 times daily, although some patients may need up to 4 puffs at a time to obtain maximum benefit during early treatment.

Children

Administration to children should be supervised by an adult.

6-12 years: One or two puffs 3 to 4 times daily

Under 6 years: One puff 3 times daily

Patients with poor inhaler technique will benefit from the consistent use of a spacer device with their metered aerosol. Use of a spacer will also decrease the amount of drug deposited in the mouth and back of the throat, and therefore reduce the incidence of local irritation in susceptible patients.

In those people using a spacer, a change in formulation of the drug used, or a change in the make of the spacer may be associated with alterations in the amount of drug delivered to the lungs. The clinical significance of these alterations is uncertain. However, in these situations, the person should be monitored for any change in their condition.

If using a spacer, the patient should be instructed to breathe in and out after each actuation of the drug into the spacer. Any delay should be kept to a minimum.

Static on the walls of the spacer may cause variability in drug delivery. Patients should be instructed to wash the spacer in warm water and detergent and allow it to dry without rinsing or drying with a cloth. This should be performed before initial use of the spacer and at least monthly thereafter.

The ATROVENT metered aerosol can must only be used with the mouthpiece supplied with the product.

OVERDOSAGE

No symptoms specific to overdosage have been encountered. In view of the wide therapeutic range and topical administration of ATROVENT inhalation solutions, no serious anticholinergic symptoms are to be expected. Minor systemic manifestations of anticholinergic action, including dry mouth, visual accommodation disorder and tachycardia may occur.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

ATROVENT is a metered dose aerosol can. It is a pressurised inhalation with a clear, colourless liquid contained in a 17 mL stainless steel can complete with mouthpiece, containing 200 metered doses, each metered dose containing 21 micrograms ipratropium bromide [equivalent to 20 micrograms ipratropium bromide (anhydrous)].

Store below 25°C.

Avoid storage in direct sunlight or heat. Do not puncture or incinerate, as canister may explode.

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

22 April 2003

DATE OF MOST RECENT AMENDMENT

29 October 2015