PRODUCT INFOMATION

APO-IPRATROPIUM SOLUTION

NAME OF THE MEDICINE

Ipratropium bromide.

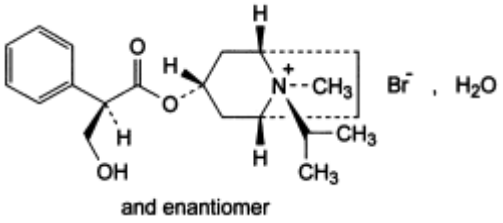
Chemical Name: (1R,3r,5S,8r)-3-[[(2RS)-3-Hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide monohydrate.

Molecular Formula: $C_{20}H_{30}NO_3Br,H_2O$

Molecular Weight: 430.4.

CAS Registry Number: 66985-17-9.

Structural Formula:



DESCRIPTION

Ipratropium bromide is an anticholinergic bronchodilator. Ipratropium bromide is a quaternary isopropyl derivative of 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 almost white crystalline powder. The powder is soluble in water, slightly soluble in ethanol and freely soluble in methanol.

PHARMACOLOGY

Pharmacodynamics

Ipratropium bromide differs essentially from the β_2-agonists in that it allows bronchodilatation by inhibiting cholinergic bronchomotor tone. That is, the vagal reflexes which mediate bronchoconstriction are blocked.

The onset of bronchodilator response with ipratropium is seen within three to five minutes of administration and peak response is reached approximately 1.5 to 2 hours after inhalation. This time course of action differs from the β_2-agonists. The duration of significant bronchodilator action with ipratropium is up to six hours.

Apo-Ipratropium and β_2-agonists may be used in combination drug therapy. There is evidence that in patients who respond to ipratropium, the concurrent administration of ipratropium and β_2-agonists results in greater relief of bronchospasm than either drug given alone. Addition of Apo-Ipratropium to the treatment regimen may enable some gradual reduction of corticosteroid dosage.

Apo-Ipratropium inhibits acetylcholine induced bronchospasm and provides partial protection against histamine and allergen induced bronchospasm. No significant change in sputum viscosity, sputum volume or mucociliary clearance has been reported.

Pharmacokinetics
No pharmacokinetic data are available on the ipratropium bromide nebulising solution. However, from limited pharmacokinetic data using an ipratropium bromide metered dose aerosol in humans, it has been shown that approximately 5% of an inhaled dose is absorbed systemically and, thus, very low plasma levels are reached. Based on this data, it may be assumed that a similar pharmacokinetic pattern applies with the ipratropium nebulising solution. However, it is suggested that the systemic levels are likely to be higher with administration of the nebulising solution due to the increased dose administered. As with other substances administered by inhalation, most of the dose enters the gastrointestinal tract, is unabsorbed and excreted in the faeces. The elimination half-life in healthy volunteers is 3.5 hours (range 1.5 to 4 hours). A total of 8 metabolites with little or no anticholinergic activity have been detected.

INDICATIONS

Apo-Ipratropium is indicated for moderate asthmatic attacks; chronic forms of asthma; asthma in patients with diminished cardiac reserve; chronic obstructive bronchitis with bronchospasm; bronchospasm during or after surgery, use during assisted ventilation with a respirator.

CONTRAINDICATIONS

Apo-Ipratropium is contraindicated in patients with a known hypersensitivity to atropine or its derivatives or to any of the ingredients in the Apo-Ipratropium preparation.

PRECAUTIONS

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

Ipratropium bromide should be used with caution in patients with prostatic hyperplasia or bladder-neck obstruction.

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angiooedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

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. Therefore, patients must be instructed in the correct handling of Apo-Ipratropium, and warned not to allow the solution to enter the eyes. The nebuliser mask must be fitted properly during inhalation.

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 and corneal congestion, may be signs of acute angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

Interactions with Other Medicines
No drug interactions have been reported with ipratropium bromide.

Ipratropium has been shown to produce effective bronchodilatation in patients receiving β-blocking agents.

Beta-adrenergics and xanthine preparations may intensify the bronchodilatory effect. The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see Precautions) may be increased when nebulised ipratropium bromide and beta-mimetics are administered simultaneously.

Use in Pregnancy (Category B1[1])
Care is recommended during pregnancy, particularly in the first trimester. Studies in rats, mice and rabbits showed no embryotoxic or teratogenic effects.

Use in Lactation
No specific studies are available to determine the excretion of ipratropium in human breast milk.

ADVERSE EFFECTS

Body as a Whole
Headache and dizziness has been reported in clinical trials with ipratropium bromide.

Cardiovascular System
Tachycardia and palpitations, supraventricular tachycardia and atrial fibrillation are anticholinergic side effects which have been reported rarely in patients known to be susceptible.

Gastrointestinal
Nausea was reported in clinical trials with ipratropium bromide. Gastrointestinal motility disturbances(e.g. constipation, diarrhoea and vomiting), an anticholinergic adverse event has been reported rarely.

Local Reactions
Dryness of the mouth or throat irritation.

Respiratory System
Cough has been reported in clinical trials with ipratropium bromide. As with other inhaled therapy, including β-agonists, paradoxical bronchoconstriction has been reported. Immediate hypersensitivity reactions may occur after administration of ipratropium bromide solution as demonstrated by rare cases of bronchospasm and oropharyngeal oedema.

Skin and Appendages
Immediate hypersensitivity reactions may occur after administration of ipratropium bromide solution as demonstrated by rare cases of urticaria(including giant urticaria), pruritus, angioedema of the tongue, lips and face, laryngospasm and rash.

Special Senses
Acute angle closure glaucoma following direct eye contact, an anticholinergic side effect has

[1] A Pregnancy Category B1 drug is defined by the Australian Drug Evaluation Committee as '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 foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage'.

been reported rarely. If the substance enters the eyes by inappropriate handling, mild and reversible disturbance of accommodation may occur. Other ocular complications have also been reported, including, mydriasis, increased intraocular pressure, eye pain.

Urogenital System
Urinary retention, an anticholinergic side effect has been reported rarely. The risk of urinary retention may be increased in patients with pre-existing outflow tract obstruction.

DOSAGE AND ADMINISTRATION

Adults
The recommended dosage is 250 to 500 µg, diluted to 2 to 3 mL with normal saline and nebulised until the entire volume of solution is inhaled, every 6 hours.

In cases of moderate bronchospasm or with assisted ventilation, a dose in the lower range of 1 mL
(250 µg) is recommended. In more severely distressed patients, 500 µg has been shown to produce optimal bronchodilatation.

Inhalation may be repeated after 2 hours.

Children
A dose of 250 µg diluted to 2 to 3 mL with normal saline is recommended for children under 12 years of age, administered in the same way as for adults.

Apo-Ipratropium can be administered via a range of commercially available nebulising devices. Where wall oxygen is available, nebulising solutions are best administered at a flow rate of 4 to 6 L/min.

Dosage is dependent on the mode of inhalation and the nebuliser used and should be adjusted to suit individual patient requirements.

Daily doses exceeding 2 mg in adults and 1 mg in children under 12 years of age should be given under medical supervision. 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.

Diluted solutions should be freshly prepared before use and any solution remaining in the nebuliser on completion of inhalation should be discarded.

OVERDOSAGE

Accidental overdose by inhalation is unlikely. Single doses of ipratropium 30 mg by mouth (equivalent to sixty 2 mL vials of Apo-Ipratropium 0.025% solution) cause anticholinergic side effects, but these are not severe and do not require specific reversal.

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

PRESENTATION AND STORAGE CONDITIONS

Apo-Ipratropium is a clear, aqueous isotonic, preservative-free nebuliser solution in single use ampoules. Each ampoule contains ipratropium bromide [equivalent to 250 µg/mL or 500 µg/mL

ipratropium bromide (anhydrous)], sodium chloride, hydrochloric acid and water for injection.

Apo-Ipratropium 250µg/1mL:
Contains 261 µg ipratropium bromide [equivalent to 250 µg ipratropium bromide (anhydrous)] in 1 mL; ampoules; 30's. AUST R 151089.

Apo-Ipratropium 500µg/1mL:
Contains 522 µg ipratropium bromide [equivalent to 500 µg ipratropium bromide (anhydrous)] in 1 mL; ampoules; 30's. AUST R 151090.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine

Date of TGA approval : 3 April 2008

Date of most recent amendment : 6 March 2009