PRODUCT MONOGRAPH

PrAtrovent®

(Ipratropium Bromide)

INHALATION AEROSOL

BRONCHODILATOR

BOEHRINGER INGELHEIM (CANADA) LTD.
5180 SOUTH SERVICE ROAD,
BURLINGTON, ONTARIO
L7L 5H4

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CONTROL NO. 083050

PRODUCT MONOGRAPH

NAME OF DRUG

Atrovent®

(Ipratropium bromide)

INHALATION AEROSOL

20 mcg/metered dose

THERAPEUTIC CLASSIFICATION

BRONCHODILATOR

ACTION AND CLINICAL PHARMACOLOGY

ATROVENT (ipratropium bromide), a quaternary ammonium derivative of atropine is an anticholinergic drug having bronchodilator properties. On inhalation the onset of action is noted within 5 to 15 minutes with a peak response between 1 and 2 hours, lasting about 2 additional hours with subsequent decline. An inhaled dose of 40 mcg induces bronchodilator effect lasting for some 6 hours.

Significant alterations on airway mucous secretion, mucociliary clearance of sputum, or gas exchange have not been observed. Systemic absorption of ATROVENT is poor and the blood levels reached are very low. Metabolic studies with ATROVENT in healthy volunteers show an average elimination half-life of 3.5 hours (range 1.5 - 4). The drug is transformed to some 8 metabolites with little or no anticholinergic activity.

In controlled 90 day studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) significant improvements in pulmonary function (FEV_1 and $FEF_{25-75\%}$ increases of 15% or more) occurred within 15 minutes, reached a

peak in 1-2 hours, and persisted for periods of 3 to 4 hours in the majority of patients and up to 6 hours in some patients.

INDICATIONS AND CLINICAL USE

ATROVENT (ipratropium bromide) is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

CONTRAINDICATIONS

ATROVENT (ipratropium bromide) inhalation aerosol is contraindicated in patients with a history of hypersensitivity to soya lecithin or related food products such as soybean and peanut. ATROVENT (ipratropium bromide) inhalation aerosol should also not be taken by patients hypersensitive to ipratropium bromide, atropinics or any other aerosol components.

WARNINGS

ATROVENT (ipratropium bromide) inhalation aerosol should not be used for the abatement of the acute episodes of bronchospasm where rapid response is required, since the drug has a slower onset of effect than that of an adrenergic β_2 agonist aerosol.

Care should be taken to ensure that ATROVENT inhalation aerosol does not reach the eye. There have been isolated reports of ocular complications (i.e., mydriasis, increased intraocular pressure, glaucoma and eye pain) when aerosolized ipratropium bromide, either alone or in combination with an adrenergic $beta_2$ agonist, has been released into the eyes. Ocular events have occurred when the aerosol was used with the standard mouthpiece or with a spacing device.

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 narrow-angle glaucoma. Should any of these symptoms develop, treatment with miotic drops should be

initiated and specialist advice sought immediately. In the event that glaucoma is precipitated or worsened, treatment should include standard measures for this condition.

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

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.

PRECAUTIONS

GENERAL

- To ensure optimal delivery of ATROVENT (ipratropium bromide) inhalation aerosol to the bronchial tree, the patient should be properly instructed by the physician or other health professional in the use of the inhaler .
- Caution is advised against the release of the aerosol into the eyes. Due care should be taken when a spacing device is employed .
- In patients with narrow-angle glaucoma, prostatic hyperplasia , urinary retention or bladder neck obstruction, ATROVENT should be used with caution .
- If a reduced response to ATROVENT becomes apparent, the patient should seek medical advice .
- Immediate hypersensitivity reactions may occur after administration of ATROVENT metered dose aerosol (see Warnings).

Like other pressurized aerosol formulations, ATROVENT inhalation aerosol contains fluorocarbon propellants trichloromonofluoromethane, dichlorodifluoromethane, 1,2-dichlorotetrafluoroethane. Such propellants may be hazardous if they are deliberately abused. Inhalation of high concentrations of aerosol sprays has brought about toxic cardiovascular effects and even death, especially under conditions of hypoxia. However, evidence attests to the relative safety of aerosols when used properly and with adequate ventilation. The

recommended dose of ATROVENT inhalation aerosol should not be exceeded and the patient should be so informed.

USE IN PREGNANCY

The safety of ATROVENT inhalation aerosol in pregnancy has not been established. The benefits of using ATROVENT when pregnancy is present or suspected must be weighed against possible hazards caused to the fetus. Studies in rats, mice and rabbits showed no embryotoxic nor teratogenic effects.

USE DURING LACTATION

No specific studies have been conducted on excretion of this drug in breast milk. Benefits of ATROVENT inhalation aerosol use during lactation should therefore be weighed against possible effects on the infant.

USE IN CHILDREN

The efficacy and safety of ATROVENT inhalation aerosol in children younger than 12 years has not been established.

DRUG INTERACTIONS

In patients receiving other anticholinergic drugs, ATROVENT should be used with caution because of possible additive effects.

Xanthine derivatives and $beta_2$ adrenergic agents may enhance the effect of ATROVENT inhalation aerosol.

ADVERSE REACTIONS

The frequency of adverse reactions reported after repeated dosing in 605 patients was as follows:

ADVERSE REACTION	NO. OF PATIENTS REPORTING (%)	
Dry mouth or throat	57	(9.4)
Headache	48	(7.9)
Bad taste	23	(3.8)
Blurred vision	19	(3.1)
Tremor	17	(2.8)
Palpitations	13	(2.1)
Urinary hesitation or retention	9	(1.5)
Dizziness	9	(1.5)
Stuffy nose	7	(1.2)
Difficulty in expectoration	4	(0.7)
Dyspnea	4	(0.7)
Nausea	3	(0.5)

There have been isolated reports of ocular events such as mydriasis, increased intraocular pressure, glaucoma and eye pain associated with the release of aerosolized ATROVENT (ipratropium bromide) into the eyes.

POSTMARKETING EXPERIENCE

World wide safety data, which includes post-marketing data, spontaneous reports, literature reports and clinical trial reports, indicates that the most frequent non-respiratory side effects of ATROVENT are: headache, nausea, dryness of mouth/throat, and bad taste.

Side effects such as tachycardia and palpitation, supraventricular tachycardia and atrial fibrillation in patients known to be susceptible, tremor, ocular accomodation disturbances, gastrointestinal motility disturbances and urinary retention are rare and reversible, although the risk of urinary retention may be increased in patients with pre-existing outflow tract obstruction.

Ocular side-effects have been reported (see Warnings).

As with other inhaled therapy including bronchodilators, cough, local irritation and in very rare instances exacerbation of symptoms and paradoxical bronchoconstriction has been observed.

Allergic-type reactions such as skin rash, angioedema of the tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported, in most of the patients who had a history of allergy to other drugs and/or foods, including soybean.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Doses of ATROVENT (ipratropium bromide) up to 1.2 mg (60 puffs) have been administered by inhalation without the appearance of serious systemic anticholinergic effects. Minor systemic manifestations of anticholinergic action, including dry mouth, visual accomodation disturbances and increase of heart rate may occur.

Should signs of serious anticholinergic toxicity appear, cholinesterase inhibitors may be considered.

DOSAGE AND ADMINISTRATION

The optimal maintenance dosage must be individually determined. The recommended dosage is 2 metered doses (actuations) (40 mcg) 3 or 4 times daily. Some patients may need up to 4 metered doses (actuations) (80 mcg) at a time to obtain maximum benefit during early treatment. The maximum daily dose should not exceed 12 metered doses (actuations) (240 mcg) and the minimum interval between doses should not be less than 4 hours.

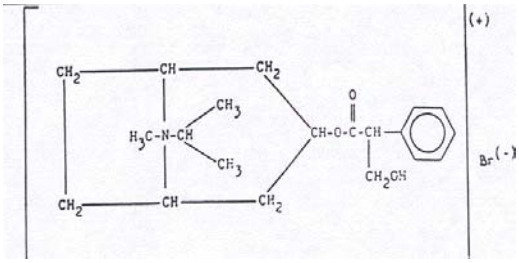
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Non-proprietary Name: ipratropium bromide

Chemical Name: (8r)-8-Isopropyl-3-(±)-tropoyloxylαH, 5αH-tropanium bromide

Structural Formula:



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

Molecular Weight: 412.37

Description: White crystalline substance with a bitter taste. Freely soluble in water and alcohol; insoluble in chloroform and ether. In neutral and acid solutions the substance is rather stable. In alkaline solutions the ester bond is rapidly hydrolyzed.

COMPOSITION

ATROVENT (ipratropium bromide) inhalation aerosol is a metered dose aerosol system which contains a suspension of ipratropium bromide monohydrate in fluorocarbon propellants (difluorodichloromethane, monofluorotrichloromethane, tetrafluorodichloroethane) with soya

lecithin as a dispersing agent. Each valve depression delivers approximately 20 mcg ipratropium bromide.

STABILITY AND STORAGE RECOMMENDATIONS

The aerosol canister should be stored at room temperature (15-30°C); the contents are stable up to the expiration date stamped on the label. Caution. Contents under pressure. Container may explode if heated. Do not place in hot water or near radiators, stoves or other sources of heat. Do not puncture or incinerate container or store at temperatures over 30°C. Keep out of reach of children.

DOSAGE FORMS

AVAILABILITY

ATROVENT (ipratropium bromide) inhalation aerosol is supplied as a metal canister containing 140 or 200 doses of ATROVENT with mouthpiece (oral adaptor). Each valve depression actuation delivers 20 mcg of ATROVENT (as a micronized powder).

INFORMATION FOR THE PATIENT

[Pr]Atrovent® (ipratropium bromide) Inhalation Aerosol

BEFORE YOU USE ATROVENT INHALATION AEROSOL, YOU SHOULD READ THIS INFORMATION LEAFLET CAREFULLY.

ATROVENT inhalation aerosol is an aerosol canister with a mouthpiece; it is used for the maintenance therapy of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema. It should not be used for the abatement of the acute episodes of bronchospasm where rapid response is required.

This information leaflet explains how to use the ATROVENT inhalation aerosol and how to avoid problems while you are using it. If you have any questions after reading this leaflet, be sure to talk to your doctor or pharmacist.

What is COPD?

COPD (Chronic Obstructive Pulmonary Disease) is a type of lung disease in which there is a permanent narrowing of the airways, leading to breathing difficulties. In many patients, this narrowing of the airways is a result of many years of cigarette smoking. Smoking cessation produces symptomatic benefits and will slow the progression of chronic bronchitis (which is a form of COPD). COPD can be helped by medication as well.

Before You Use ATROVENT Inhalation Aerosol:

Be sure to tell your doctor:

- if you are pregnant or intend to become pregnant;
- if you are breast feeding;
- if you have any other health problems;
- if you have eye problems, such as glaucoma, or eye pain;

- if you are taking any other medications including those you can buy without a prescription;
- if you have any allergies or reactions to foods, drugs or aerosols. This includes allergies to soya lecithin or related food products such as soybean and peanut.

How To Use Your ATROVENT Inhalation Aerosol:

DO NOT exceed the number of puffs prescribed by your doctor. DO NOT use the inhaler more often than your doctor recommends.

- The usual dose is 2 puffs taken up to 3 or 4 times daily. Some people may need up to 4 puffs at a time during early treatment. Do not use more than 12 puffs per day unless your doctor has told you to do so.

- If your symptoms get worse, contact your doctor immediately. While taking ATROVENT inhalation aerosol, other inhaled medications should be used only as prescribed by your physician.

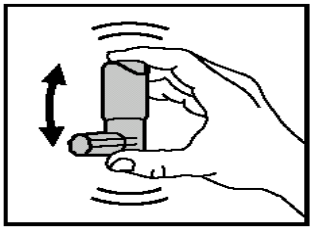
- If you are troubled with mucus try to clear your chest as completely as possible by coughing before you use ATROVENT inhalation aerosol. This will allow the ATROVENT inhalation aerosol to pass more deeply into your lungs.

- Before you start to use ATROVENT inhalation aerosol, read the following instructions carefully; be sure that you know how to use the inhaler properly. If you use the inhaler incorrectly, you may not be getting all of the medication you need. If you have any questions about using the inhaler, check with your doctor .

- The plastic mouthpiece has been especially designed for use with ATROVENT inhalation aerosol to ensure that you always get the right amount of the medicine. The mouthpiece must never be used with any other inhalation aerosol nor must the ATROVENT inhalation aerosol be used with any mouthpiece other than the one supplied with the product.

1. Remove the protective cap from the inhaler.

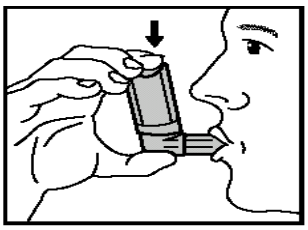
2. The inhaler should be shaken and the canister depressed twice before the inhaler is initially used.



3. Shake the unit well, as shown.

4. Breathe out as completely as possible.

   a) Place the mouthpiece into your mouth and close your lips around it. Keep your teeth apart and your tongue flat to allow free flow of the medication into your lungs.



   b) Press the canister down into the mouthpiece and breathe in deeply through your mouth at the same time.

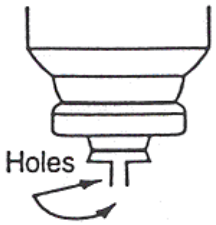
5. Hold your breath for a few seconds, then breathe out slowly.

6. If your doctor has recommended a second puff, wait about one minute and then repeat steps , 3, 4 and 5.

7. Replace the protective plastic cap.

Care of the Mouthpiece/Canister

The mouthpiece should be washed with warm water once a week. You must remove the mouthpiece from the canister before you begin to clean the mouthpiece. If you use soap or detergent, the mouthpiece should be well rinsed in clear water, and then allowed to air dry. The mouthpiece must be completely dry before you put the canister back into the mouthpiece.



Sometimes, the canister stem may also get dirty or blocked. Pull the canister out of the mouthpiece and check the small holes in the stem. If these two small holes seem blocked, rinse them with clear lukewarm water. When the canister is dry, put it back into the mouthpiece.

Since it is not possible to see when the contents are used up, shaking the inhaler will allow you to determine if there is any remaining fluid in the canister.

Please Remember

1. ATROVENT inhalation aerosol has been prescribed to treat *your* current condition. DO NOT give it to other people.

2. DO NOT take any other medication without your doctor's advice. Tell any *other* doctor, dentist, or pharmacist with whom you consult that you are using ATROVENT inhalation aerosol.

3. **When using your ATROVENT inhalation aerosol with the standard mouthpiece or with a spacer device, make sure you do not spray the aerosol into your eyes.**

4. Like any drug product, ATROVENT inhalation aerosol may cause unwanted effects along with the good effects. If you do experience any unusual or unwanted effects while you are using ATROVENT you should contact your doctor.

5. Consult your doctor immediately if you experience any of the following:

   ·Increased wheezing or tightness in the chest;

- Swelling of the tongue or lips;
- Difficulty in swallowing;
- Fast or irregular heart beat;
- Blurred vision or pain in the eyes;
- Difficult or painful urination;
- Skin rash

6. If you experience a dry mouth or bad taste, sucking on a sour candy or rinsing your mouth may help. Check with your doctor if the dry mouth or bad taste persist or if you experience constipation for a prolonged period of time.

7. **Keep this medication out of the reach of children.**

8. Keep from freezing.

9. Container may explode if heated. Contents under pressure. Do not place in hot water or near radiators, stoves, or other sources of heat. Do not puncture or incinerate container or store at temperatures over 30°C.

Non-medicinal ingredients (in alphabetical order): propellants 11, 12, 114, soya lecithin.

PHARMACOLOGY

Ipratropium bromide (ATROVENT) is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In preclinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of cyclic guanosine monophosphate (cyclic GMP) caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.

When it is delivered by aerosol, ATROVENT exerts its effects primarily in the bronchial tree, thereby demonstrating a local, site specific effect, and not a systemic one.

When administered to the guinea pig and dog intravenously at an ED_{50} of 0.15-0.40 mcg/kg, ATROVENT abolishes acetylcholine induced bronchospasm with a transient effect on blood pressure. By inhalation, approximately 25 mcg of ipratropium bromide produces a 50% inhibition of acetylcholine induced bronchospasm in the dog with no detectable effect on blood pressure but with an increased duration of action compared to i.v. administration. Histological evaluation of human bronchial mucosa following chronic inhalation of ipratropium bromide showed no alterations of epithelial, ciliated or goblet cells. Short term mucociliary clearance in normal and bronchitic subjects was not adversely affected by 200 mcg of inhaled ipratropium bromide.

The anticholinergic effects of ipratropium bromide were evaluated in several other organ systems following oral, subcutaneous, intravenous and inhalation administration. In dogs, a 50% increase in heart rate resulted from an s.c. dose of about 0.011 mg/kg, equipotent to atropine, but the equi-effective oral dose of ipratropium was 58 times greater. By inhalation no increase in heart rate or pathological changes in ECG pattern were recorded at doses up to 8 mg. In another experiment, blood pressure and heart rate in the dog could be modulated after i.v. administration of low doses of ipratropium bromide, but metered aerosol administration of 100 puffs (40 mcg/puff) was required to produce an 11% increase in heart rate.

Salivary secretion in rat, mouse and dog was effectively inhibited by low parenteral doses of ipratropium bromide (0.001 to 0.032 mg/kg) but when given by the oral route, the effective dose

increased over 100-fold. Aerosol administration in dogs of about 65 puffs (0.04 mg/puff) produced a 50% inhibition of salivary flow. Similarly, effects on gastric secretion in the rat showed at least a 100-fold difference between effective enteral and subcutaneous doses.

Mydriatic effects of ipratropium bromide in mice were approximately equipotent to atropine after s.c. doses but were 10-20 times less after oral administration. Tests of doses of ipratropium bromide up to 100 mg/kg in the rabbit showed no effect on the central nervous system.

Ipratropium bromide, subcutaneously, inhibited the secretory effects of the cholinergic agonist, oxtremorine, in mice. It also exhibited spasmolytic effects equivalent to or greater than atropine in isolated guinea pig gut. In vitro tests with the isolated rectum of the guinea pig demonstrated the effectiveness of ipratropium bromide in suppressing the spasmogenic effects of acetylcholine and pilocarpine. It was ineffective against histamine or barium chloride induced spasm. Ipratropium bromide exerted anticholinergic effects on the in situ bladder and intestine preparations of the dog. Intravenous doses were 500 times more potent than oral or intraduodenal administration.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Ipratropium bromide is absorbed very quickly after oral inhalation. The peak plasma concentrations are reached only minutes after inhalation.

The basic pharmacokinetic parameters were calculated from the plasma level data after i.v. administration. A rapid biphasic decline in plasma is noted for ipratropium. The half-life of the terminal elimination phase was about 1.6 hours. The half-life for elimination of the drug and metabolites was 3.6 hours, as determined after radio-labeling. The main metabolites found in urine bind poorly to the muscarinic receptor. The total clearance of the active ingredient is 2.3 L/minute. Approximately 40% of the clearance is renal (0.9 L/min) and 60% non-renal, i.e. mainly hepato-metabolic. The volume of distribution (Vz) is 338 L (corresponding to approx. 4.6 L/kg).

Plasma concentrations after inhaled ipratropium bromide were about 1000 times lower than equipotent oral or i.v. doses (15 and 0.15 mg, respectively).

Renal excretion of the active ingredient is given as 46% of the dose after intravenous administration and 8% of the dose after inhalation of an aerosol.

The drug is minimally (less then 20%) bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier, consistent with the quaternary amine structure of the molecule .

Up to 8 metabolites of ipratropium bromide have been detected in man, rat and dog. In man, about 70% of the drug is excreted unchanged after i.v. administration and only one metabolite exceeds 10% of the total radioactivity. The elimination occurs primarily via the kidney with less than 10% of the total intravenous dose excreted via the biliary or fecal route. After oral or inhaled doses, however, up to 90% of the dose is detectable in the feces, suggesting poor absorption.

PHARMACODYNAMICS

Large, single inhaled doses of ATROVENT have been given to man without any signs of toxicity. After the administration of 400 mcg to 10 normal subjects no changes were detected in pulse rate, blood pressure, intraocular pressure, salivary secretion, visual accommodation or electrocardiograms. Likewise, in another study, no changes in pulse rate or salivary secretion were seen when cumulative doses up to 1.2 mg were administered by inhalation to 12 normal volunteers.

Special studies utilizing normal therapeutic doses in asthmatic and chronic bronchitic patients again have not revealed any systemic anticholinergic effects.

In one study, 14 patients were treated for 45 days with either ATROVENT 40 mcg q.i.d. or ATROVENT 40 mcg q.i.d. plus oral Berotec 5 mg q.i.d. No changes in visual acuity, intraocular pressure, pupil size or accommodation of vision occurred. Micturition function studies in 20 male patients showed no differences in urinary flow, total flow time and time until maximum flow between placebo and ATROVENT 40 mcg t.i.d administered for 3 days.

A wide variety of challenge studies have been conducted utilizing ATROVENT as a protective agent. In pharmacologically induced bronchospasm, ATROVENT, in clinical doses, was very effective against methacholine and acetylcholine, moderately effective against propranolol but had little or no effect against histamine or serotonin. Studies in exercise induced bronchospasm have yielded variable results. Some investigations have indicated that ATROVENT has little or no effect but other studies have shown that some patients, at least, are protected against bronchospasm induced by exercise. Likewise, the protective effects of ATROVENT against cold air induced bronchospasm have been variable.

Antigen challenge studies have demonstrated that ATROVENT offers some protection against the "early" allergic asthma response, but has no effect on the "late" response.

TOXICOLOGY

ACUTE

Acute toxicity has been investigated with observation periods of 14 days in several rodent and non-rodent species.

SPECIES	SEX	ROUTE	LD50 (mg/kg)
Mouse		i.v.	13.5
Mouse	M	i.v.	12.3
Mouse	F	i.v.	15.0
Mouse		s.c.	322
Mouse		s.c.	300
Mouse		oral	2050
Mouse		oral	1038
Rat		i.v.	15.8
Rat		s.c.	1500
Rat		oral	>4000
Rat		oral	1722
Dog		i.v.	17.5

The signs of toxicity were apathy, reduced mobility, ataxia, paralysis of skeletal muscle, clonic convulsions and death from respiratory failure. Toxic signs persisted for 3 hours after i.v. and 8 days after oral administration. The rather low oral toxicity compared to the higher intravenous toxicity reflects the poor gastro-intestinal absorption.

Acute dose tolerance studies were performed in dogs. No deaths occurred up to doses of 400 mg/kg oral or 50 mg/kg s.c. Signs of toxicity were mydriasis, dryness of oral, nasal and optic mucosa, vomiting, ataxia, increased heart rate, decreased body temperature and death from respiratory failure.

When administered by inhalation, the minimum lethal dose in the guinea pig was 199 mg/kg and in rats dosed of 11.5 mcg/L/hr q.i.d. or 48 mcg/kg/4 hours did not cause mortality. The oral and intravenous LD_{50} were considerably higher than the minimum lethal dose by inhalation.

Anesthetized normal and hypoventilated dogs tolerated doses up to 200 puffs (4 mg) of ipratropium bromide without ECG changes or heart failure. Reductions in heart rate were observed. Similar findings were seen in dogs given i.v. infusions (10 mg/kg/min.) up to 1550 mg/kg or 1000 mg/kg plus 200 puffs from a placebo inhaler. Blood pressure reductions were also seen in these experiments.

SUBACUTE

Oral

A subacute toxicity study of 9 weeks duration in rats utilizing doses of 10, 100 and 500 mg/kg revealed no pathological findings apart from a dose related decrease in food consumption and growth rate.

A 4 week study in dogs using doses of 3, 30 and 150 (for 3 weeks) increased to 300 mg/kg showed mydriasis, inhibition of lacrimal and salivary secretion, tracheal and ocular inflammation, decreased food intake and weight loss at the medium and high doses. Three of 6 dogs died when the dose was increased from 150 to 300 mg/kg.

A supplementary study of 13 weeks using doses of 1.5, 3.0 and 15 mg/kg revealed no pathological changes apart from a dose related inhibition of lacrimation and associated keratoconjunctivitis and dryness of the mouth.

Subcutaneous

Rats were treated with subcutaneous injections of 1, 10 and 100 mg/kg. One death occurred in the 10 mg/kg dose group from paralytic ileus. Inflammatory changes were noted at the injection site.

A 4 week study in dogs using doses of 10, 20 and 30 mg/kg (increased to 40 mg/kg on the last 5 days) was conducted. Dryness of the oral and nasal mucous membranes and mydriasis were noted along with conjunctivitis and keratitis associated with decreased lacrimal secretions. A decrease in food intake and body weight also occurred. One dog died in the high dose group. Signs of liver damage were noted in 2 high dose dogs. Low testicular weights, which have not been observed in other subsequent studies, were also observed.

Inhalation

Twelve rats were exposed to aerosolized ipratropium bromide in a concentration of 11.5 mcg/L for 1 hour, 4 times per day for 7 days. No drug toxicity was found.

In another study, administration of ipratropium bromide in doses of 128, 256 and 384 mcg per rat per day for 30 days showed no signs of toxicity apart from a low grade inflammatory response and areas of fibrosis and hemorrhage in the parametrium of 2/9 females in the high dose group. This finding has not been observed in subsequent studies.

Four rhesus monkeys inhaled 500 mcg of ipratropium bromide twice a day (total dose 1 mg/day) for 7 days without the appearance of any drug induced toxicity.

In another study rhesus monkeys were given ipratropium bromide in doses of 200, 400 and 800 mcg/day by inhalation for 6 weeks. Included in the tests were measurements of mucociliary transport rate and ciliary beat frequency. No signs of drug toxicity were found.

CHRONIC

Oral

A 6 month and a 1 year study in rats using doses of 6, 30 and 150 mg/kg were performed. The high dose was increased to 200 mg/kg after l4 weeks. Reductions in food consumption and growth rates were observed in the highest dose group. A dose dependent constipation which caused severe coprostasis and dilatation of the intestines was observed in the highest dose groups. A toxic hepatosis was observed in some animals of the highest dose group.

Ipratropium bromide was administered to dogs in doses of 1.5, 3.0, 15.0 and 75.0 mg/kg for 1 year. A decrease in body weight development was seen in the highest dose group and food consumption was reduced in the dogs receiving 3 mg/kg and above. Emesis was seen in all treated groups. A dose dependent decrease (3 mg/kg and above) in nasal, oral and lacrimal secretions, the latter leading to keratoconjunctivitis was observed. Increases in SGPT and SGOT (15 and 75 mg/kg) and alkaline phosphatase (75 mg/kg) were noted. Localized gastric necrosis was found in 2 dogs at the highest dose and a non-dose-dependent fatty degeneration of the liver which varied from animal to animal, was also seen.

Inhalation

In inhalation studies up to 6 months in rats, dogs and rhesus monkeys, the no-observed adverse effect level (NOAEL) was 0.384 mg/kg/day, 0.4 mg/kg/day and 0.8 mg/kg/day respectively. Histopathologically, no substance-related lesions were observed in the broncho-pulmonary system. The only finding was a dose related decrease in growth rate in male rats. In the rat the oral NOAEL after 18 months administration was 0.5 mg/kg/day.

An aqueous solution of ATROVENT (48 mcg/kg/4 hours) was locally well tolerated when administered to rats by inhalation.

Neither active anaphylaxis nor passive cutaneous anaphylactic reactions were demonstrated in guinea pigs.

MUTAGENICITY

In vitro mutagenicity on bacteria (Ames test) did not indicate a mutagenic potential. The results of in vivo assays (micronucleus test, dominant lethal test in mice, cytogenic assay on bone marrow cells of Chinese hamsters), did not demonstrate an increase in rate of chromosomal aberrations.

CARCINOGENICITY

Carcinogenicity studies in mice (107 weeks duration) and rats (114 weeks duration) utilizing oral doses up to 6 mg/kg were performed. These studies demonstrated that ipratropium bromide does not have a tumorgenic or carcinogenic effects.

REPRODUCTIVE STUDIES

Studies to investigate the possible influence of ATROVENT on fertility, embryo-fetotoxicity, and peri/postnatal development have been performed on mice, rats and rabbits.

Even the highest oral dose levels employed (1000 mg/kg/day in the rat and 125 mg/kg/day in the rabbit), which proved to be maternotoxic, did not induce malformations in the offspring.

In an inhalation teratology study the highest, technically feasible doses for inhalation of the metered aerosol, 1.5 mg/kg/day in rats and 1.8 mg/dg/day in rabbits, showed no adverse effects on litter parameters, and no embryotoxic or teratogenic effects.

A fertility study in rats with oral doses of 5, 50 and 500 mg/kg being given 60 days prior to and during early gestation was performed. Fertility was delayed in 8 of 20 couples at 500 mg/kg and spurious pregnancy in 5 of 20 females occurred at this dose. In addition, the conception rate was decreased in 75% of females at this dose. No embryotoxic or teratogenic effects were observed.

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