PRODUCT MONOGRAPH

MYLAN-SALBUTAMOL RESPIRATOR SOLUTION

(Salbutamol Sulphate Inhalation Solution)

5 mg/mL

Bronchodilator

Mylan Pharmaceuticals ULC
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Etobicoke, Ontario
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Date of Preparation:
June 9, 2009

Control#: 130472

NAME OF DRUG

MYLAN-SALBUTAMOL RESPIRATOR SOLUTION

(Salbutamol Sulphate Inhalation Solution)

5 mg/mL

THERAPEUTIC CLASSIFICATION

Bronchodilator, $beta_2$-adrenergic stimulant

CLINICAL PHARMACOLOGY

Salbutamol produces bronchodilation through stimulation of $beta_2$-adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of muscle fibers. This action is manifested by an increase in pulmonary function as demonstrated by spirometric measurements. A measurable decrease in airway resistance is typically observed 5 to 15 minutes after inhalation of salbutamol. The onset of maximum improvement in pulmonary function usually occurs after 60 to 90 minutes, and significant bronchodilator activity has been maintained from 3 to 6 hours.

INDICATIONS AND CLINICAL USE

Treatment of severe bronchospasm associated with exacerbations of chronic bronchitis and bronchial asthma. It can be used by "wet" nebulization. When administered through a nebulizer, it should be used with compressed air or oxygen.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients and in patients with cardiac tachyarrhythmias. Respirator solution use in children under 5 has not been established.

WARNINGS

In accordance with the present practice for asthma treatment, concomitant anti-inflammatory therapy should be part of the regimen if salbutamol respirator solution needs to be used on a regular daily basis (see DOSAGE AND ADMINISTRATION).

Pregnancy and Lactation: The safety of salbutamol in pregnancy and in lactation has not been established.

In common with other β-adrenergic agents, salbutamol can induce reversible metabolic changes. These are most pronounced during infusions of the drug and include hyperglycemia and hypokalemia. Potentially serious hypokalemia may result from β_2-agonist therapy, mainly from parenteral and nebulized administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and hypoxia. Hypokalemia will increase the susceptibility of digitalis-treated patients to cardiac arrhythmias (see Precautions). It is recommended that serum potassium levels be monitored in such situations. Large doses of i.v. salbutamol have been reported to aggravate pre-existing diabetes mellitus and precipitate ketoacidosis. Concurrent administration of corticosteroids can exaggerate this effect. The relevance of these observations to the use of salbutamol respirator solution is unknown.

Special care and supervision are required in patients with idiopathic hypertrophic subvalvular aortic stenosis, in whom an increase in the pressure gradient between the left ventricle and the aorta may occur, causing increased strain on the left ventricle.

Beta-adrenergic blocking drugs, especially the non-cardioselective ones, may effectively antagonize the action of salbutamol and produce bronchospasm resistant to salbutamol injection. Therefore, salbutamol and non-selective beta-blocking drugs, such as propranolol, should not usually be prescribed together.

Care should be taken in patients suffering from cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension; in patients with convulsive disorders, diabetes mellitus or hyperthyroidism and in patients who are usually responsive to sympathomimetic amines.

Some patients have been reported to have developed severe paradoxical bronchospasm with repeated excessive use of sympathomimetic inhalation preparations. The cause of this refractory state is unknown. It is advisable that in this event the use of the preparation be discontinued immediately and alternate therapy instituted, since in the reported cases the patients did not respond to other forms of therapy until the drug was withdrawn.

Fatalities have been reported following the excessive use of inhaled sympathomimetic drugs, the exact cause of which is unknown; however, cardiac arrest following the unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. Therefore, it is essential that the physician instruct the patient in the need for further evaluation if the patient's asthma becomes worse. In individual patients, any β_2-adrenergic agonist, including salbutamol, may have a clinically significant cardiac effect.

It has been reported that the use of intermittent positive pressure ventilation (IPPV) in acute asthma attacks, in several cases was related to lethal episodes of hypoxia and pneumothorax. This method of drug administration may be ineffective in patients with severe obstruction and greatly increased airway resistance and it may induce severe hypercapnia and hypoxia. During IPPV therapy, the monitoring of arterial blood gases is highly desirable.

Salbutamol respirator solution should be administered with extreme caution to patients being treated with MAO inhibitors or tricyclic antidepressants since the action of salbutamol on the cardiovascular system may be potentiated.

Immediate hypersensitivity reactions including angioedema, urticaria, bronchospasm, anaphylaxis, hypotension, rash, oropharyngeal edema and collapse have been reported very rarely.

PRECAUTIONS

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

Failure to respond for at least 3 hours to a previously effective dose of salbutamol indicates a deterioration of the condition and the physician should be contacted promptly. Patients should be warned not to exceed the recommended dose.

Increasing the use of β_2-agonists is usually a sign of worsening asthma. Under these conditions it is inadequate simply to increase their use in particular over an extended period of time, and a reassessment of the patient's therapy plan is required and concomitant anti-inflammatory therapy should be considered.

To ensure the proper dosage administration of the drug, the patient should be instructed by the physician or other health professional in the proper use of the nebulizer. During inhalation, children should be assisted or supervised by an adult who knows the proper use of the nebulizer.

Use of the respirator solution by means other than nebulization or IPPV is not recommended until the safety and the dosage regimen for alternate methods of delivery have been established.

Drug Interactions: Salbutamol should be administered with extreme caution to patients being treated with MAO inhibitors or tricyclic antidepressants since the action of salbutamol on the cardiovascular system may be potentiated.

The concomitant use of salbutamol and other sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving salbutamol tablets. Such concomitant use, should be individualized, and not given on a routine basis. If regular co-administration is required, this indicates that disease control is suboptimal and alternative therapy should be considered.

Salbutamol and beta-receptor blocking agents inhibit the effect of each other.

A small number of cases of acute angle closure glaucoma have been reported in patients treated with a combination of nebulized salbutamol and ipratropium bromide. A combination of nebulised salbutamol with nebulized anticholinergics should therefore be used cautiously. Patients should receive adequate instruction in correct administration and be warned not to let the solution or mist enter the eye.

Pregnancy: *Teratogenic Effects:* Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Salbutamol has been in widespread use for many years in human beings without apparent ill consequence; however, as with the majority of drugs, there is little published evidence of its safety in the early stages of human pregnancy; there are no adequate and well-controlled studies in pregnant women. Salbutamol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human aerosol dose; when given s.c. in doses corresponding to the human nebulization dose; when given s.c. in doses corresponding to 0.2 times the maximum human (child weighing 21 kg) oral dose; and when given s.c. in doses corresponding to 0.4 times the maximum human oral dose.

Labor and Delivery: Salbutamol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It has been reported that high doses of salbutamol administered i.v. inhibit uterine contractions. Although this effect is extremely unlikely as a consequence of the use of inhaled formulations, it should be kept in mind. Oral salbutamol has been shown to delay preterm labor in some reports. There are presently no well-controlled studies which demonstrate that it will stop preterm labor or prevent labor at term. Therefore, cautious use of salbutamol is required in pregnant patients when given for relief of bronchospasm so as to avoid interference with uterine contractibility.
As maternal pulmonary edema has been reported during or following premature labor in patients receiving β_2-agonists, careful attention should be given to fluid balance, and cardio-respiratory function should be monitored.

Lactation: As salbutamol is probably secreted in breast milk and because of the potential for tumorigenicity shown in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

ADVERSE REACTIONS

The most frequent adverse reactions are nervousness and tremor. Headache, tension due to effects on skeletal muscle, tachycardia, palpitations, transient muscle cramps, insomnia, nausea, weakness, dizziness and sweating have also been reported. Other rare adverse events have been drowsiness, flushing, restlessness, irritability, chest discomfort, difficulty in micturition, hypertension, angina, vomiting, vertigo, central nervous stimulation, unusual taste and drying or irritation of the oropharynx.

As with other β_2-agonists, hyperactivity has been reported rarely in children.

Potentially serious hypokalemia may result from β_2-agonist therapy, mainly from parenteral and nebulized administration.

Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension, rash, oropharyngeal edema and collapse have been reported very rarely.

As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage may cause tachycardia, cardiac arrhythmia, hypokalemia, hypertension and, in extreme cases, sudden death. In order to antagonize the effect of salbutamol, the judicious use of a cardioselective beta-adrenergic blocking agent (e.g. metoprolol, atenolol), may be considered, bearing in mind the danger of inducing an asthmatic attack. Serum potassium levels should be monitored.

DOSAGE AND ADMINISTRATION

Dosage should be individualized, and patient response should be monitored by the prescribing physician on an ongoing basis.

If a previously effective dose fails to provide the usual relief, or if the effects of a dose last for less than three hours, patients should seek medical advice immediately since this is usually a sign of seriously worsening asthma.

In accordance with the present practice for asthma treatment, concomitant anti-inflammatory therapy should be part of the regimen if salbutamol respirator solution needs to be used on a regular daily basis.

Adults: The average dose for a single treatment is 2.5 mg to 5 mg Salbutamol up to 4 times daily.

Children: 5 to 12 years: The average dose for a single treatment is 1.25 to 2.5 mg Salbutamol. (See PHARMACEUTICAL INFORMATION).

For more refractory cases, the single dose may be increased to 5 mg of salbutamol. Treatment may be repeated 4 times a day, if necessary.

If a more severe attack has not been relieved by a treatment, further treatment may be required. In these cases, patients should immediately consult their doctor or the nearest hospital. Increasing demand for salbutamol respirator solution in bronchial asthma is usually a sign of worsening asthma and indicates that the treatment plan should be reviewed.

Mylan-Salbutamol Respirator Solution is to be used with a respirator or nebulizer, only under the direction of a physician.

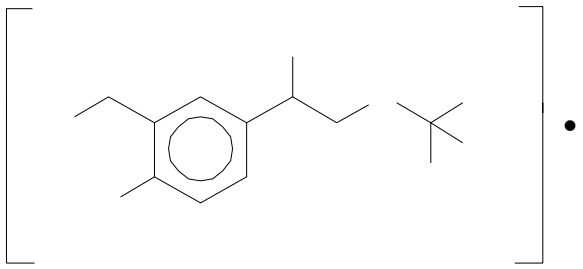
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Salbutamol sulphate

Chemical Name: 1,3-Benzenedimethanol, α1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-sulfate.

Chemical Structure:



Molecular Formula: $C_{26}H_{44}N_2O_{10}S$

Molecular Weight: 576.7

Description: A white odourless powder soluble 1:4 in water and slightly soluble in alcohol, chloroform, and ether. pH=5.8 (1% solution)

Composition:

Mylan-Salbutamol Respirator Solution is a sterile solution containing salbutamol sulphate equivalent to 5 mg of salbutamol base per mL. The solution is preserved with benzalkonium chloride 0.01% w/v (5 mg/mL). The pH is adjusted with sulfuric acid.

Stability and Storage Recommendations:

Store between 15˚ and 25˚C. Protect from light.

In hospitals, diluted Mylan-Salbutamol Respirator Solution (5 mg/mL), usually 1:5 or 1:10, with Sterile 5% Dextrose, or Sterile Normal Saline, should be used within 24 hours from time of dilution when stored at room temperature or within 48 hours when stored under refrigeration.

In the home, Mylan-Salbutamol Respirator Solution (5 mg/mL) should be diluted with Sterile Normal Saline immediately before use.

Special Instructions:

Mylan-Salbutamol Respirator Solution can be used by 2 methods:

1) Nebulization.
2) Intermittent positive pressure ventilation.

Nebulization

When used in a nebulizer, a mouthpiece or a face mask may be applied. The nebulizer should be connected to a compressed air or oxygen pump. Gas flow should be approximately 6 to 10 L/minute. With an average volume of 3 mL, a single treatment lasts approximately 10 minutes. It is advisable to prepare one dose at a time.

In hospitals, diluted Mylan-Salbutamol Respirator Solution (5 mg/mL), usually 1:5 or 1:10, with Sterile Normal Saline, should be used within 24 hours from time of dilution when stored at room temperature or within 48 hours when stored under refrigeration.

Diluents containing preservatives are not recommended as the safety of preservatives have not been established for inhalation therapy.

Cleansing and maintenance of the nebulizer must be carefully followed according to the manufacturer's instructions.

Intermittent positive pressure ventilation

When administered through intermittent positive pressure ventilation, the inspiratory pressure is usually 10-20 cm H_20 and the duration of administration varies from 5 to 20 minutes, depending upon the patient and the control of the apparatus. This length of administration provides a more gradual and more complete lysis of bronchospasm. It has been reported that the use of intermittent positive pressure ventilation in acute asthma attacks, in several cases was related to lethal episodes of hypoxia and pneumothorax. This method of drug administration may be ineffective in patients with severe obstruction and greatly increased airway resistance and it may induce severe hypercapnia and hypoxia.

During intermittent positive pressure ventilation therapy, the monitoring of arterial blood gases is highly desirable.

AVAILABILITY OF DOSAGE FORMS

Sterile Mylan-Salbutamol Respirator Solution contains salbutamol sulphate equivalent to 5 mg of salbutamol base per mL. The 5 mg/mL solution is preserved with benzalkonium chloride 0.01% w/v, and is available in glass containers of 10 mL.

INFORMATION FOR THE PATIENT

MYLAN-SALBUTAMOL RESPIRATOR SOLUTION: 5 mg/mL

- *Directions for use of Mylan-Salbutamol Respirator Solution at home.*
- *Please read this insert carefully before you start your medicine. For further information or advice, ask your doctor or pharmacist.*
- *You may want to read this insert again. PLEASE DO NOT THROW IT AWAY until you have finished your medicine.*

INTRODUCTION

Your doctor has prescribed a medicine called Mylan-Salbutamol Respirator Solution (salbutamol sulphate) to you. Mylan-Salbutamol Respirator Solution is a bronchodilator medicine that your doctor has chosen to suit you and your condition. It can relieve chest tightness and wheezing if you have asthma or another chest illness. Mylan-Salbutamol Respirator Solution works by relieving spasm in the small air passages in the lungs and so helps to ease breathing problems. Please follow these instructions carefully. It is important that you use your Mylan-Salbutamol Respirator Solution properly to ensure that you receive the maximum benefit from your medicine.

PRECAUTIONS

Use your Mylan-Salbutamol Respirator Solution only as directed by your doctor. He will tell you how often, and how much to take for a treatment. If you are not sure how much or when to take your medicine, ask your doctor or pharmacist. The action of Mylan-Salbutamol Respirator Solution may last up to 6 hours and should last at least 4 hours. **Call your doctor immediately if the effect of your usual dose lasts for less than three hours or if you suddenly get worse shortness of breath and you wheeze after using your Mylan-Salbutamol Respirator Solution**. Do not increase the dose or how often you take your medicine without informing your doctor. If symptoms get worse, tell your doctor as soon as possible.

When using Mylan-Salbutamol Respirator Solution, other medicines (including asthma medicines) should only be used when prescribed by your doctor.

IMPORTANT POINTS TO NOTE BEFORE TAKING YOUR MEDICINE

1. Have you ever had to stop taking another medication for this illness because you were allergic to it or because it caused problems?

2. Are you having treatment for a thyroid condition?

3. Are you having treatment for raised blood pressure or a heart problem?

If the answer is YES to any of these questions tell your doctor or pharmacist as soon as possible if you have not already done so.

Very occasionally some people feel a little shaky or have a headache after using Mylan-Salbutamol Respirator Solution. Muscle cramps can occur although these are quite rare. These effects usually wear off with continued treatment. Tell your doctor but do not stop using the medicine unless told to do so.

If you accidentally take a LARGER DOSE THAN PRESCRIBED you may notice that your heart is beating faster than usual and that you feel shaky. These effects usually wear off within a few hours but you should tell your doctor as soon as possible.

In the event of an EXCESSIVE overdosage tell your doctor without delay or contact your hospital or nearest poison control centre.

Your doctor may decide not to prescribe this medicine during the first three months of pregnancy, nor if you are breast feeding a baby. However, there may be circumstances when your doctor advises you differently.

REMEMBER: This medicine is for YOU only. Only your doctor can prescribe it for you. NEVER give it to someone else. It may harm that person even if his/her symptoms are the same as yours.

CHILDREN

Mylan-Salbutamol Respirator Solution should be used under the supervision of an adult who understands the proper use of the nebulizer, and only as prescribed by the doctor.

DOSAGE

An effective treatment with Mylan-Salbutamol Respirator Solution should last at least four hours. **Call your doctor immediately if the effect of your usual dose lasts for less than three hours. If you regularly use Mylan-Salbutamol Respirator Solution two or more times per day, and take no other asthma medication, you should talk to your doctor who may want to reassess your treatment plan.**

Adults: Mylan-Salbutamol Respirator Solution 0.5 to 1.0 mL (2.5 to 5.0 mg of salbutamol) should be diluted in 2 to 5 mL or more of sterile normal saline. Treatment may be repeated four times a day if necessary.

Children (5_12 years): The average dose for a single treatment is 0.25 to 0.5 mL of Mylan-Salbutamol Respirator Solution (1.25 to 2.5 mg of salbutamol) diluted in 2 to 5 mL or more of sterile normal saline. For more refractory cases, the single dose of Mylan-Salbutamol Respirator Solution may be increased to 1 mL (5 mg of salbutamol). Treatment may be repeated four times a day if necessary.

DIRECTIONS FOR USE

Mylan-Salbutamol Respirator Solution contains salbutamol 5 mg per mL. For proper administration, 1 mL of the solution is usually diluted with 2 to 5 mL of sterile normal saline.

In the home, Mylan-Salbutamol Respirator Solution may be diluted immediately before use. Pre_diluted solutions of Mylan-Salbutamol Respirator Solution should not be stored. BEFORE STARTING TREATMENT WITH THIS DRUG, BE SURE THAT YOU ARE FULLY FAMILIAR WITH THE USE AND PROPER CARE OF YOUR NEBULIZER.

1. When preparing the solution for inhalation, use a graduated syringe to draw up Mylan-Salbutamol Respirator Solution from the bottle at the dose directed by your physician. NOTE: Close the Mylan-Salbutamol Respirator Solution bottle as soon as the solution is drawn into the syringe. Keep the bottle closed at all times and do not open it unnecessarily. Discard unused, diluted Mylan-Salbutamol Respirator Solution after each use.

2. Inject the solution into the nebulizer through the appropriate opening.

3. Draw into the syringe the amount of diluting fluid (sterile normal saline) directed by your physician and add it to the nebulizer.

4. Gently shake the nebulizer and connect it with the mouthpiece or face mask.

5. Connect the apparatus to the air pump or oxygen and start the treatment.

6. Breathe calmly and evenly as much as possible until no more mist is formed in the nebulizer chamber. At this point, treatment is finished.

7. Any unused solution in the respirator should be discarded.

AFTER TAKING YOUR MEDICINE

If you notice a sudden worsening of your shortness of breath and wheeze shortly after taking your medicine, tell your doctor as soon as possible.

If the relief of wheezing or chest tightness is not as good as usual, tell your doctor as soon as possible. It may be that your chest condition is worsening and you may need to add another type of medicine to your treatment.

CARE OF THE MYLAN-SALBUTAMOL RESPIRATOR SOLUTION AND NEBULIZER

Cleaning: After each use, clean the syringe and nebulizer as instructed in the nebulizer manual or as follows:

To Clean the Nebulizer:

1. Disassemble the supply tube and the nebulizer.

2. Wash in warm detergent solution. Rinse the tube with water.

3. To wash the suction tubes:

    a) Place 3 mL of detergent solution in the vial, assemble the unit and operate for 2 minutes.

    b) Disassemble and rinse the vial with warm water, place 3 mL of warm water in the vial, assemble the unit and operate for 2 minutes.

    c) Disassemble and rinse with warm water.

4. To dry the external passage:

    a) Connect the nebulizer tube to the pump with the supply tube.

    b) Turn on the pump and blow air through for 1 minute.

5. If there is evidence of clogging, clean the openings and tube connectors with the detergent, then rinse with water.

6. Reassemble.

To Clean the Syringe:

1. Clean the syringe and needle several times in detergent solution by alternatively drawing up and expelling the detergent solution.

2. Repeat using a rinse of warm water.

3. Dry the needle by drawing air into the syringe several times, by moving the plunger back and forth in the barrel of the syringe. Remove the needle.

4. Remove the plunger from the syringe, allow to air dry.

5. Keep unassembled needle, plunger and barrel of syringe wrapped in clean tissue, stored in a refrigerator along with the Mylan-Salbutamol Respirator Solution bottle.

Discard any solution left in the nebulizer after you finish treatment, clean and dry the nebulizer as instructed by the nebulizer manual.

Follow all the instructions of the nebulizer and air pump manufacturers for the proper care and maintenance of the apparatus.

Do NOT swallow or inject Mylan-Salbutamol Respirator Solution. The solution is inhaled into your lungs using a nebulizer.

FURTHER INFORMATION

If you have any questions or are not sure about anything to do with your medicine, then you should ask your doctor or pharmacist.

PHARMACOLOGY

Animal studies

Several *in vitro* and *in vivo* studies have demonstrated the relatively selective action of salbutamol on the β_2-adrenergic receptors of the bronchial and vascular smooth muscles.

In anesthetized guinea pigs, salbutamol completely prevents acetylcholine-induced bronchospasm at the dose of 100 µg/kg intravenously.

In anesthetized dogs, salbutamol is one-fifth as potent as isoprenaline in skeletal muscle vasodilation.

In the isolated atrium preparation of guinea pigs, salbutamol was 500 to 2500 times less potent than isoprenaline in increasing the rate and force of contraction, respectively. Administration of salbutamol aerosol at the dose of 250 µg/mL for one minute to guinea pigs, prevented acetylcholine-induced bronchospasm without any effect on the heart rate.

In anesthetized cats and dogs, salbutamol prevented the bronchospasm elicited by vagal stimulation, without any significant effect on heart rate and blood pressure.

Comparative tests of salbutamol and isoprenaline muscle, and human heart muscle, have shown that the effect of salbutamol on beta-adrenergic receptors in the heart is minimal. In 6 dogs with right-sided cardiac bypass, salbutamol, given at the dose of 25 µg/mL, improved left ventricular efficiency and increased coronary blood flow. In-vitro studies have shown that salbutamol produces dose-related inhibition of histamine release from passively sensitised human lung fragments which was antagonized by propranolol.

Human Studies

Administration of 10 mg salbutamol as a 0.5% solution through IPPV from a Bennett ventilator, given in a 3 minute period, resulted in a 40% increase of FEV_1, with maximal effect occurring after about 90 minutes. The heart rate had an average increase of 9 beats/minute, peaking after 25 minutes, and lasting for about 36 minutes. No ECG changes were observed.

In a long term study, salbutamol solution 0.5% was self-administered at home via a portable nebulizer, without IPPV, by 28 adult patients with severe chronic asthma. The dose was 0.5 mL (2.5 mg salbutamol) in 4.5 mL normal saline, 2 to 4 times daily, and the duration of treatment ranged from 0.9 to 2.7 years (mean 1.7 years). For each patient the treatment period was compared retrospectively with a control period of the same duration preceding nebulizer therapy. No statistically significant differences between treatment and control periods were found for pulmonary function tests performed before and after 5 puffs of a salbutamol pressurized aerosol, or for number of out-patient emergency department visits, hospitalizations, sick leaves, and days

hospitalized. However, there were significant reductions during the treatment period in the duration of sick leaves and medical ward treatments, while 50% of the patients reported that it was easier to sleep and two-thirds said it was easier to exercise.

In 10 pediatric studies, a total of 189 patients up to 14 years of age were treated with salbutamol solution 0.5% administered via a portable nebulizer. In most cases, the dose was between 0.5 mL and 1.0 mL per treatment, diluted with normal saline, bringing the total volume to 2.0 mL. Children with asthma had very good results from the treatment, while children with bronchitis or bronchiolitis were less responsive. Salbutamol was very well tolerated in these studies. One author reported 2 cases of skeletal muscle tremor, but drew attention to the fact that both patients received concurrent oral bronchodilator. Otherwise, the only reported side effect was an occasional mild tachycardia.

Human Pharmacokinetics and Metabolism

Five asthmatic patients were given tritium labelled salbutamol from the nebulizer of an intermittent positive pressure ventilator. A rapid initial rise in plasma concentration of total radioactivity was observed in all patients. In 4 of the 5 patients, there was a further rise in plasma concentration to a peak at 2 to 4 hours. All patients showed an improvement in FEV_1 with peak improvement occurring at 30 minutes to 2 hours. An average 12.5% of the initial dose was recovered in the urine. Of the radioactivity recovered, 88% was recovered in the first 24 hours. The metabolite in the urine was the same as that found in the plasma. During the first 2 hours, the ratio of free salbutamol to metabolite averaged 2:1, whereas by 8 hours, the ratio was 9:11, and this reversed ratio was maintained thereafter.

TOXICOLOGY

Acute Toxicity

		LD_{50} (mg/kg)	
Species (n)	Oral	Intravenous	Intraperitoneal
Mouse (10)	>2000	72	--
Rat: Adult (10)	>2000	60	--
Rat: Newborn (155)	--	--	216
Rat: Weanling (100)	--	--	524
Rat: 6-weeks (90)	--	--	437

Animals that died had convulsions and cyanosis. Death occurred mostly within 4 hours after administration. Respiration first increased, then decreased to abnormally slow and deep. Rabbits, cats and dogs survived a single oral dose of 50 mg/kg salbutamol.

Intermediate (Four Months) Toxicity

Rat: Salbutamol was given p.o. from 0.5 mg/kg up to 25 mg/kg daily on an increasing scale. There were no significant hematological changes except a small increase in hemoglobin and packed cell volumes. BUN and SGOT values were elevated while blood glucose and plasma protein levels remained unchanged. Pituitaries had increased amount of PAS-positive material in the cleft at higher dose levels.

Dog: Salbutamol was given twice daily, in oral doses from 0.05 mg/kg to 12.5 mg/kg, on an increasing scale. Hemoglobin and packed cell volume were slightly decreased, particularly at higher doses. Leukocyte count decreased after 16 weeks of treatment at each dose level. Platelet count was increased after 8 weeks at the highest dose. No significant effects were seen on biochemical values. The only significant histological change was the appearance of corpora almyacea in the stomach, attributed to altered mucus secretion. Inhalation of 1000 μg of salbutamol aerosol for 3 months did not produce any morphological changes in lungs, trachea, lymph nodes, liver and heart.

Long-term Toxicity

Chronic toxicity studies were carried out in 2 separate centres. Fifty female, Charles River CD Albino rats received salbutamol orally at 2, 10, and 50 mg/kg/day for 104 weeks: 50 female Charles River CD Sprague-Dawley derived rats received orally 20 mg/kg/day for 50 weeks, and 50 female Charles River Long-Evans rats received orally 20 mg/kg/day for 96 weeks. These studies demonstrated a dose-related incidence of mesovarium leiomyomas. No similar tumors were seen in mice.

Mutagenicity

In-vitro tests involving 4 different micro-organisms revealed no mutagenic activity.

Carcinogenicity

In a two-year study in the rat, salbutamol caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at doses corresponding to 111, 555, and 2,800 times the maximum human inhalation dose. The relevance of these findings to human is not known. An 18-month study in mice revealed no evidence of tumorigenicity.

Teratogenicity Studies

Rat: No adverse effect was seen when salbutamol was given orally at 0.5, 2.32, 10.75 and 50 mg/kg/day throughout pregnancy. When given to 2 consecutive generations at doses up to 50 mg/kg/day, no adverse effect was observed on the reproductive function of either male or female rats. The only toxic effect was an increase in neonatal mortality in the highest dose level group. All the progeny that died showed obvious signs of lack of parental care.

Rabbit: A reproductive study in rabbits revealed cranial malformations in 37% of foetuses at 50 mg/kg/day, 70 times the maximum human oral dose.

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