VENTOL

Respiratory Solution

Composition
Each ml of Ventol solution for inhalation contains 5 mg Salbutamol (as sulphate).

Action
Salbutamol is a short-acting, relatively selective $beta_2$-adrenoceptor agonist. Administration by inhalation results in direct stimulation of $beta_2$-adrenoceptors in bronchial smooth muscle and hence bronchodilation. This is thought to be due to stimulation of adenyl cyclase by salbutamol, resulting in increased levels of cyclic AMP within cells. These are thought to inhibit the entry of calcium ions into the cells, thus inhibiting smooth muscle contraction. High levels of cyclic AMP in mast cells may also inhibit the release of histamine and slow reacting substance-A (SRS-A).

After administration of salbutamol, stimulation of both $beta_1$- and $beta_2$-adrenoceptors occurs because $beta_2$ selectivity is not absolute. This results in the $beta_1$ effect of cardiac stimulation, though not so much as with isoprenaline, and $beta_2$ effects of peripheral vasodilation and hypotension, skeletal muscle tremor and uterine muscle relaxation. Stimulation of $beta_2$-adrenoceptors can result in changes in serum levels of glucose, insulin, and potassium.

Pharmacokinetics

Absorption

Following inhalation of salbutamol, the onset of action is 5-15 minutes. Only 10-20% of the dose reaches the lungs, the remainder stays in the mouth, stomach or on the apparatus. Salbutamol reaching the lungs acts rapidly and directly on bronchial smooth muscle. Initially, the drug is undetectable in blood but after 2-3 hours, low concentrations are seen due presumably to the portion of the dose that is swallowed and absorbed by the gut.

Distribution

Salbutamol is not bound to plasma proteins.

Metabolism

The major metabolite of salbutamol, recovered from urine, has been identified as the 4'-o-sulfate ester. This metabolite has negligible beta stimulant activity. Salbutamol is not metabolised in the lung and the pattern of metabolism and excretion (as well as absorption) suggests that most aerosol is swallowed. The half-life is between 2.7-5 hours.

Excretion

Following inhalation of salbutamol 77%-97% of the dose recovered in the urine after 48 hours, 45-60% as the 4'-o-sulfate ester and the rest as unchanged salbutamol. A small fraction is excreted in the faeces.

Indications
Ventol solution for inhalation is indicated for the relief of bronchospasm in patients 2 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm.

Contraindications
Salbutamol solution for inhalation is contraindicated in patients with a history of hypersensitivity to Salbutamol or any of its components.

Warnings
Paradoxical Bronchospasm

Salbutamol solution for inhalation can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Salbutamol solution for inhalation should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical

bronchospasm, when associated with inhaled formulations, frequently occurs with the first- use of a new canister or vial.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs and with the home use of nebulizers, it is therefore essential that the physician instruct the patient in the need for further evaluation if his/her asthma becomes worse.

Cardiovascular Effects
Salbutamol solution for inhalation, like all other β-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms.
Although such effects are uncommon after administration of Salbutamol solution for inhalation at recommended doses, if they occur, the drug may need to be discontinued. In addition, β-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QT, interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Salbutamol solution for inhalation, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma
Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Salbutamol solution for inhalation than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g.: corticosteroids.

Immediate Hypersensitivity Reactions
Immediate hypersensitivity reactions may occur after administration of Salbutamol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

Use of Anti-Inflammatory Agents
The use of β-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids.

Microbial Contamination
To avoid microbial contamination, proper aseptic technique should be used each time the bottle is opened. Precautions should be taken to prevent contact of the dropper tip of the bottle with any surface, including the nebulizer reservoir and associated ventilatory equipment. In addition, if the solution changes color or becomes cloudy, it should not be used.

Adverse Reactions

Central nervous system
Tremors, Dizziness, Nervousness, Headache, Sleeplessness

Gastrointestinal
Nausea, Dyspepsia

Ear, nose, and throat
Nasal congestion, Pharyngitis

Cardiovascular
Tachycardia, Hypertension

Respiratory
Bronchospasm, Cough, Bronchitis , Wheezing

Precautions

General

Salbutamol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmia, in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any β-adrenergic bronchodilator. Large doses of intravenous Salbutamol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

As with other β-agonists, Salbutamol may produce significant hypokalemia in some patients, possibly through intracellular shunting, this has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.
Repeated dosing with 0.15 mg/kg of Salbutamol inhalation solution in children aged 5 to 17 years who were initially normokalemic has been associated with an asymptomatic decline of 20% to 25% in serum potassium levels.

Pregnancy

Category C
There are no adequate and well-controlled studies in pregnant women. Salbutamol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with Salbutamol some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between Salbutamol use and congenital anomalies has not been established

Use in Labor and Delivery

Because of the potential for β-agonist interference with uterine contractility, use of Salbutamol solution for inhalation for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis

Salbutamol has not been approved for the management of preterm labor. The benefit: risk ratio when Salbutamol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with β2-agonists, including Salbutamol.

Nursing Mothers

It is unknown whether this drug is excreted in human milk 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.

Pediatric Use

The safety and effectiveness of Salbutamol solution for inhalation have been established in children 2 years of age and older.
The safety and effectiveness of Salbutamol solution for inhalation in children below 2 years of age have not been established

Drug Interactions

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with Salbutamol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants
Salbutamol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of Salbutamol on the vascular system may be potentiated.

B-Blockers
B-adrenergic receptor blocking agents not only block the pulmonary effect of β-agonists, such as Salbutamol solution for inhalation, but also may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with β-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of β-adrenergic blocking agents in patients with asthma. In this setting, cardioselective β-blockers could be considered, although they should be administered with caution.

Diuretics
The ECG changes and/or hypokalemia that may result from the administration of non potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by β-agonists, especially when the recommended dose of the β-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co administration of β-agonists with non- potassium-sparing diuretics.

Digoxin
Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of Salbutamol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving Salbutamol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and Salbutamol.

Dosage and Administration
To avoid microbial contamination, proper aseptic techniques should be used each time the bottle is opened. Precautions should be taken to prevent contact of the dropper tip of the bottle with any surface, including the nebulizer reservoir and associated ventilatory equipment. In addition, if the solution changes color or becomes cloudy, it should not be used.

Children 2 to 12 Years of Age
For children 2 to 12 years of age initial dosing should be based upon body weight (0.1 to 0.15 mg/kg per dose), with subsequent dosing titrated, achieve the desired, clinical response. Dosing should not exceed 2.5 mg three to four times daily by nebulization the following table outlines approximate dosing according to body weight. The appropriate volume of the 0.5% inhalation solution should be diluted in sterile normal saline solution to a total volume of 3 ml prior to" administration via nebulization.

Approximate Weight (kg)	Approximate Weight (Ib)	Dose (mg)	Volume of Inhalation Solution
10-15	22-33	1.25	0.25 ml
>15	>33	2.5	0.50 ml

Adults and Children Over 12 Years of Age
The usual dosage for adults and children over 12 years of age is 2.5 mg of Salbutamol administered three to four times daily by, nebulization. More frequent administration or higher doses are not recommended. To administer 2.5 mg of Salbutamol, dilute 0.5 ml of the 0.5% inhalation solution with 2.5 ml of sterile normal saline solution the flow rate is regulated to suit the particular nebulizer so that Ventol solution for inhalation will be delivered over approximately 5 to 15 Minutes.

The use of Ventol Inhalation Solution can be continued as medically indicated to control recurring bouts of bronchospasm. During this time, most patients gain optimal benefit from regular use of the inhalation solution.

If a previously effective dosage regimen fails to provide the usual relief medical advice should be Bought immediately, as this is often a sign of seriously worsening asthma that , would require reassessment of therapy, Drug compatibility (physical and chemical) efficacy and safety of Ventol solution for inhalation when mixed with other drugs in a nebulizer have not been established.

Over Dosage

Overdosage of inhaled salbutamol may produce significant tachycardia and/or significant muscle tremor.

Treatment: The specific antidote for overdosage with salbutamol is a cardio-selective beta-blocking agent given by intravenous injection. IN GENERAL, BETA-BLOCKING DRUGS SHOULD BE USED WITH CAUTION AS THEY MAY CAUSE BRONCHOSPASM IN SENSITIVE INDIVIDUALS.
Hypokalaemia may occur following overdosage with salbutamol. Serum potassium levels should be monitored.

Presentation

Glass bottle of 20 ml