PRODUCT MONOGRAPH

ORCIPRENALINE

Orciprenaline Sulphate Syrup
House Standard

2 mg/mL

β_2-Adrenergic Stimulant
Bronchodilator

AA PHARMA INC.
1165 Creditstone Road, Unit #1
Vaughan, Ontario
L4K 4N7

DATE OF PREPARATION:
April 10, 2014

Control Number: 172362

PRODUCT MONOGRAPH

ORCIPRENALINE

Orciprenaline Sulfate Syrup

House Standard

2 mg/mL

THERAPEUTIC CLASSIFICATION

β_2–Adrenergic Stimulant

Bronchodilator

ACTIONS AND CLINICAL PHARMACOLOGY

Orciprenaline sulphate is a bronchodilating agent. The bronchospasm associated with various pulmonary diseases - chronic bronchitis, pulmonary emphysema, bronchial asthma, silicosis, tuberculosis, sarcoidosis and carcinoma of the lung, has been successfully reversed by therapy with orciprenaline sulphate.

Orciprenaline sulphate has the following major characteristics:

1) Pharmacologically, the action of orciprenaline sulphate is one of beta stimulation. Receptor sites in the bronchi and bronchioles are more sensitive to the drug than those in the heart and blood vessels, so that the ratio of bronchodilating to cardiovascular effects is favourable. Consequently, it is usually possible clinically to produce good bronchodilation at dosage levels which are unlikely to cause cardiovascular side effects.

2) The efficacy of the bronchodilator after both oral and inhalation administration has been demonstrated by pulmonary function studies (spirometry, and by measurement of airways resistance by body plethysmography).

3) Rapid onset of action follows administration of orciprenaline sulphate inhalants, and the effect is usually noted immediately. Following oral administration, the effect is usually noted within 30 minutes.

4) The peak effect of bronchodilator activity following orciprenaline sulphate generally occurs within 60 to 90 minutes, and this activity lasts for 3 to 6 hours.

5) Orciprenaline sulphate taken orally potentiates the action of a bronchodilator inhalant administered 90 minutes later, whereas no additive effect occurs when the drugs are given in reverse order.

6) Patients have not developed tolerance to the drug during prolonged therapy.

7) No toxic effects on the liver, kidneys or hematologic system have been reported in the long–term use of orciprenaline sulphate in man.

INDICATIONS AND CLINICAL USE

Orciprenaline sulphate has been found useful in the following conditions:

- Bronchial asthma
- Chronic bronchitis
- Pulmonary emphysema

Orciprenaline sulphate is also useful in sarcoidosis, silicosis, carcinoma of the lung and tuberculosis when bronchospasm contributes to the disability.

The efficacy of orciprenaline sulphate has been demonstrated by improvement of flow rates (FEV_1, MMFR, MEFR) and airways resistance measurements (body plethysmography). Repeated measurements of pulmonary function made over a 4–hour period show that orciprenaline sulphate 20 mg orally gives a generally better result regarding duration of action and magnitude of response than placebo, 100 mg methoxyphenamine, 30 mg ephedrine by mouth, or 10 mg isoproterenol sublingually.

The effect of an inhalant bronchodilator may be potentiated by oral administration of 20 mg of orciprenaline sulphate 90 minutes prior to use of the inhalant. No additive effect occurs when the drugs are given in reverse order. The probable reason for this is that a bronchodilator delivered to the lungs via the vascular system (intravenous or oral medication) acts upon bronchioles whether or not they are occluded. Such an effect causes a wider distribution in the lungs of a subsequently given drug, and consequently the bronchodilation is more intense. Knowledge of this interaction is of value when instructing patients in the combined use of oral and inhalant forms of orciprenaline sulphate.

Orciprenaline sulphate may be given orally in dosages ranging from 60 mg to 120 mg daily. An effective clinical response in adults and children above 12 years can be achieved by 20 mg orciprenaline sulphate 3 times daily, and at this dosage side effects are not significantly different from those following placebo. Orciprenaline sulphate at a dosage of 20 mg 4 times daily is well tolerated and side effects are usually mild. Only at dosages of 100 mg daily and above, do palpitations and tremulousness become troublesome. If high doses of orciprenaline sulphate are

necessary, it may be possible to eliminate the side effects whilst continuing the same total daily dose, by administering 10 mg single doses at more frequent intervals.

The low incidence of side effects together with effective bronchodilation make orciprenaline sulphate acceptable to patients with chronic bronchial asthma for continuous use either alone or concurrently with corticosteroids. Some of these patients may be controlled with orciprenaline sulphate as the sole medication, and it may be possible to avoid the use of steroid therapy. In a proportion of individuals who are already taking corticosteroids, it may be possible to withdraw this medication and continue with orciprenaline sulphate alone. However, caution should be observed in this regard as many patients, particularly those with severe bronchial asthma, can be managed satisfactorily only if steroids and bronchodilators are given together.

Prolonged studies have shown that patients with bronchitis and emphysema respond to continuous therapy with orciprenaline sulphate. The frequency and severity of acute attacks decrease, and patients experience relief of wheezing, chest congestion and shortness of breath. A close association is apparent between objective measurements of pulmonary function and the subjective response.

CONTRAINDICATIONS

Known sensitivity to the drug or other sympathomimetic amines. The use of ORCIPRENALINE (orciprenaline sulphate) and other beta stimulators is generally considered to be contraindicated in patients with hypertrophic obstructive cardiomyopathy and cardiac arrhythmias associated with tachycardia.

Beta–blocking agents, e.g., propranolol, effectively antagonize the action of ORCIPRENALINE. Their concomitant use, except in the treatment of accidental overdosage, is therefore contraindicated.

ORCIPRENALINE should not be taken in patients with a history of hypersensitivity to the active ingredient or other components of the product.

WARNINGS

Like other β_2 agonists, ORCIPRENALINE (orciprenaline sulphate) should not be used on a regular daily basis without appropriate concomitant anti-inflammatory therapy (see DOSAGE AND ADMINISTRATION).

ORCIPRENALINE should not be administered to pregnant women or to women of childbearing potential unless in the opinion of the physician the expected benefits outweigh the possible risks to the fetus. In rabbits, high oral doses (100 mg/kg) and low subcutaneous doses (0.2 mg/kg) have resulted in malformed offspring in some experiments, but not in others. Studies in the rat, mouse and rhesus monkey have shown no adverse effects on the developing fetus. Other sympathomimetic drugs tested, viz., ephedrine and phenylephrine, produced teratogenic effects in the rabbit when given orally at high doses as did isoproterenol given subcutaneously at low doses. The significance of these findings is not known.

However, clinical evidence presently available from the use of ORCIPRENALINE in pregnancy is limited. β_2–agonists should be used with caution before childbirth in view of their inhibiting effect on uterine contractions.

Care should be taken in patients suffering from myocardial insufficiency, cardiac arrhythmias, recent myocardial infarction, severe organic heart and/or other vascular disorders, hypertension, hyperthyroidism phaeochromocytoma or diabetes mellitus.

Occasional patients have been reported to have developed severe paradoxical airways resistance with repeated excessive use of sympathomimetic inhalation preparations. The cause of this refractory state is unknown. It is advisable that in such instances 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 excessive use of isoproterenol inhalation preparations and the exact cause is unknown. Cardiac arrest was noted in several instances.

Patients should be advised to seek medical aid in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol. The failure to respond may be due to retention of viscid bronchial secretions, associated with an allergic or infective exacerbation of the patient's condition. Increased airways resistance on the basis of bronchospasm alone is reversed promptly by bronchodilators and, if this does not occur, a more serious condition should be suspected. Admission to hospital for intensive support of the cardiovascular and respiratory systems may be necessary.

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 may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics; the adverse effects of hypokalemia on cardiac rhythm may be exacerbated by hypoxia. It is recommended that serum potassium levels be monitored in such situations. Hypokalemia will increase the susceptibility of digitalis–treated patients to cardiac arrhythmias.

PRECAUTIONS

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 dyspnea, a doctor should be consulted immediately.

Increasing use of $ß_2$–agonists to control symptoms of bronchial obstruction, especially administration on a regular basis or in high amounts, indicates deterioration of asthma control. Under these conditions, the patient's therapy plan has to be revised. It is inadequate simply to increase the use of bronchodilators under these circumstances, in particular over extended periods of time (see DOSAGE AND ADMINISTRATION).

In acute tests, orciprenaline sulphate has been shown to have minimal effect on blood pressure and pulse. The drug should be used with care, however, in asthmatic or emphysematous patients who also have systemic hypertension, coronary artery disease, acute and recurring congestive heart failure, diabetes mellitus, glaucoma or hyperthyroidism or in patients sensitive to sympathomimetic amines.

DRUG INTERACTIONS

Concomitant use of orciprenaline sulphate with other sympathomimetic agents is not recommended since the combined use may lead to deleterious cardiovascular effects. If concomitant use is necessary, this should take place only under strict medical supervision.

Extreme care must also be exercised in the concomitant use of orciprenaline sulphate with epinephrine, monoamine oxidase inhibitors or tricyclic antidepressants since the action of beta adrenergic agonists may be enhanced.

Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effects of beta-agonists.

PREGNANCY

There is no well documented experience in pregnant women. Orciprenaline sulphate should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus.

LACTATION

It is not known whether orciprenaline sulphate is excreted in human milk; therefore, orciprenaline sulphate should be used during nursing only if the potential benefit justifies the possible risk to the newborn.

ADVERSE REACTIONS

In the recommended dosage, the most frequently observed adverse reactions to orciprenaline sulphate include, fine tremor of skeletal muscles, nervousness, headache, dizziness, tachycardia, and palpitations.

As with other beta-mimetics, nausea, vomiting, sweating, weakness and myalgia/muscle cramps may occur. In rare cases decrease in diastolic blood pressure, increase in systolic blood pressure, arrhythmia, particularly after higher doses, may occur.

In rare cases skin reactions or allergic reactions have been reported, especially in hypersensitive patients. There have been isolated cases of anaphylactic or anaphylactoid reactions.

In individual cases psychological alterations have been reported under inhalational therapy with beta-mimetics.

Potentially serious hypokalemia may result from β_2-agonist therapy.

As with use of other inhalation therapy, cough, local irritation, and less common, paradoxical bronchoconstriction have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The symptoms of overdosage are those of excess beta stimulation including exaggeration of the known pharmacological effects, i.e. any of the symptoms listed under adverse reactions, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias, and flushing.

Therapy may include administration of sedative, tranquilizers or in severe cases, intensive therapy.

Beta-receptor blockers, preferably $beta_1$-selective, are suitable as specific antidotes; however, a possible increase in bronchial obstruction must be taken into account and the dose should be adjusted carefully in patients suffering from asthma. If has been shown that the beta-blocker propranolol effectively antagonizes the action of orciprenaline sulphate and the use of this agent should be considered under these circumstances.

DOSAGE AND ADMINISTRATION

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

If a previous effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is a sign of seriously worsening asthma that requires reassessment of therapy.

In accordance with the present practice for asthma treatment, concomitant anti-inflammatory therapy should be part of the regimen when a β_2-agonist needs to be used on a regular daily basis.

The following recommended dosages represent general guidelines that are suitable for the majority of patients.

Syrup:

Adult Dosage:	20 mg (10 mL) t.i.d. or q.i.d.	
Pediatric Dosage:	Ages 4-12:	10 mg (5 mL) t.i.d
	Above 12:	20 mg (10 mL) t.i.d.

PHARMACEUTICAL INFORMATION

Drug Substance

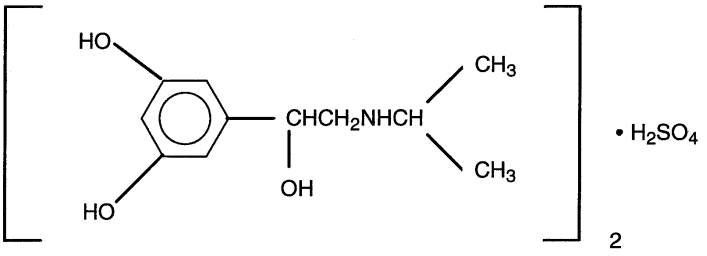
Common Name: Orciprenaline sulphate (metaproterenol sulfate USP)

Chemical Names:

1) 1,3-Benzenediol,5-[1-hydroxy-2-[1-methylethyl)-amino] ethyl]-,sulfate (2:1)(salt);

2) 3,5-Dihydroxy-α-[(iso-propylamino)methyl]benzyl alcohol sulfate (2:1).

Structural Formula:



Molecular Formula: $(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4$

Molecular Weight: 520.60

Description: White to off–white crystalline powder, freely soluble in water.

Composition

Each mL of ORCIPRENALINE (orciprenaline sulphate) syrup contains 2 mg orciprenaline sulphate (metaproterenol sulfate USP). Each mL also contains artificial grape flavour, edetate disodium, glycerin, hydroxyethyl cellulose, methylparaben, propylparaben, purified water, and sorbitol.

Stability and Storage Recommendations

ORCIPRENALINE syrup should be stored at room temperature (15-30°C). Protect from light.

AVAILABILITY OF DOSAGE FORMS

ORCIPRENALINE (orciprenaline sulphate) syrup is clear and grape–flavoured. Each mL contains 2 mg of active ingredient orciprenaline sulphate (Metaproterenol Sulfate USP). Available in amber–coloured bottles containing 250 mL of clear syrup.

INFORMATION FOR THE PATIENT

ORCIPRENALINE (Orciprenaline sulphate) Syrup has been found useful in the following conditions:

– Bronchial asthma (condition of the lungs in which there is widespread narrowing of airways)

– Chronic bronchitis (chronic inflammation of one or more bronchi usually secondary to infection)

– Pulmonary emphysema (pathological accumulation of air in the lungs)

ORCIPRENALINE Syrup is also useful in other conditions like: sarcoidosis (chronic inflammatory lesions), silicosis (inflammation of the lung caused by foreign bodies), lung cancer and tuberculosis (TB - infection caused by bacteria) when a significant narrowing of the airways (bronchospasm) is present.

When ORCIPRENALINE Syrup is taken as directed by your doctor, you will note easier breathing within 20 to 30 minutes, and this effect will persist for 3 to 6 hours. When taken as directed, orciprenaline sulphate often produces a reduction in frequency and severity of acute episodes of

involuntary muscle contractions of the lungs (bronchospastic attacks), a corresponding relief of wheezing, chest congestion and shortness of breath.

ORCIPRENALINE Syrup is useful in all patients who have difficulty in swallowing tablets, but is particularly suitable for children and geriatric patients. ORCIPRENALINE Syrup has a pleasant taste.

Helpful reminders for patients with chronic bronchospastic disorders

The following factors can sometimes significantly influence your ability to breathe efficiently. Your doctor has, undoubtedly, discussed with you those points which are important in your case. It is essential that you follow his advice meticulously.

1) If your doctor suggests breathing exercises or postural drainage, follow his directions carefully. Breathing exercises help increase the strength, coordination and efficiency of the breathing muscles, and postural drainage helps to remove the extra fluid (mucus) from the lungs.

2) If your doctor recommends a reducing diet, follow it closely since being overweight makes breathing more difficult.

3) Should you have allergies to certain foods, inhalants or drugs, avoidance of these factors may prove most beneficial.

4) Overwork, nervous tension and inadequate sleep all contribute to fatigue. Care should be taken to ensure an adequate amount of rest.

5) Coughs, colds and the “flu” frequently cause acute breathing difficulties (bronchospasm) in the asthmatic or bronchitic patient. Considerable care should be taken to avoid contact with persons having cold or “flu” symptoms and should you develop a cold, consult your doctor as soon as possible.

6) The winter months can present additional problems for patients with breathing difficulties. As much as possible, sudden temperature changes should be avoided. When venturing outside, the use of a scarf or handkerchief over the nose and mouth is advisable. It is also important that correct air humidification be maintained within your dwelling, particularly during the winter months.

7) Certain irritants in the air cannot be avoided completely because of their seasonal or environmental presence; however, all measures should be taken to reduce exposure to these substances. The inhalation of tobacco smoke can and should be avoided. Dust control measures such as frequent household vacuuming and changing of furnace filters may prove helpful.

Important Warnings

Patients should seek medical aid in the event that they do not respond to their usual dose of ORCIPRENALINE.

Serious And Common Side Effects

In the recommended dosage, the most frequently observed side effects to orciprenaline sulphate include shakes, nervousness, headache, dizziness, rapid or irregular heart beats.

Potentially serious low level of potassium in the blood may result from taking this type of medication (β_2-agonist).

Symptoms And Treatment Of Overdosage

The symptoms of overdosage include any of the symptoms listed under the section “Serious and Common Side Effects”, with the most noticeable being high or low blood pressure, irregular or rapid heart beats, chest pain, trembling and flushing of the face.

If you have accidentally taken too much of ORCIPRENALINE, contact your doctor or nearest hospital emergency department immediately, even if you do not feel sick. If you go to the doctor or the hospital, take the ORCIPRENALINE container with you.

Precautions

1) Persons with high blood pressure, heart disease, diabetes, glaucoma or thyroid disease should use ORCIPRENALINE only on the advice of a doctor.

2) Patients should inform their doctor if they are pregnant, planning to become pregnant or breastfeeding.

3) Patients should inform their doctor of all drugs that they may take including prescription, non-prescription, and herbal products.

4) Patients should inform their doctor if they’ve ever had an allergic reaction to any ingredient of ORCIPRENALINE.

Dosage

Patients should follow their doctor's instructions about when and how to take ORCIPRENALINE. The dosages listed below are doses usually recommended.

Children:	Ages 4-12:	10 mg (5 mL or one teaspoonful) three times daily;
	Above 12:	20 mg (10 mL or two teaspoonfuls) three times daily.
Adults:		20 mg (10 mL or two teaspoonfuls) three or four times daily.

Availability

ORCIPRENALINE Syrup is available in amber coloured bottles containing 250 mL of clear syrup.

Storage

Store at room temperature (15-30°C) and protect from light.

Medicinal and Nonmedicinal Ingredients

Each mL of ORCIPRENALINE (orciprenaline sulphate) syrup contains 2 mg orciprenaline sulphate (metaproterenol sulfate USP). Each mL also contains artificial grape flavour, edetate disodium, glycerin, hydroxyethyl cellulose, methylparaben, propylparaben, purified water, and sorbitol.

PHARMACOLOGY

Bronchodilator Action

In guinea–pigs and dogs, orciprenaline sulphate has a marked relaxing effect on bronchospasm induced by histamine, acetylcholine, or serotonin. When administered orally, orciprenaline sulphate protects guinea–pigs from histamine–induced asthma. In dogs, orciprenaline sulphate is better absorbed and acts longer than isoproterenol. In dogs in which bronchospasm has been induced with morphine or pilocarpine, 1 mg/kg isoproterenol and 30 mg/kg orciprenaline sulphate administered intravenously, have the same degree of bronchodilator action; however, the effect of orciprenaline sulphate lasts considerably longer than that of isoproterenol.

Effect on Muco–ciliary Transport

The rate of clearance of colloidal silver iodide from rat lung *in vivo* was not adversely affected by orciprenaline sulphate aerosol. Nor did orciprenaline sulphate interfere with muco–ciliary transport in a rabbit tracheal preparation *in vitro.*

Cardiovascular Effects

Orciprenaline sulphate administered intravenously to anesthetized dogs in equivalent bronchodilator doses tends to have less effect on blood pressure and heart rate than isoproterenol. In dogs, with small intravenous doses there is occasionally a fall in diastolic pressure and, because of the increase in the cardiac output, there is an increase in systolic pressure with a consequent increase in pulse pressure. The ratio between intramuscular and oral effects is 1:67 for orciprenaline sulphate and 1:333 for isoproterenol. Thus the oral absorption of orciprenaline sulphate in dogs is approximately 5 times better than that of isoproterenol.

In various isolated heart preparations, orciprenaline sulphate has positive inotropic and chronotropic effects. In the spontaneously beating right atrium (cat) a dose of orciprenaline sulphate 41 times greater than that of isoproterenol is required to achieve the same inotropic effect but with electrically stimulated atrium and papillary muscle, concentrations only 1.2 and 2.7 times greater were required respectively. Thus in heart preparations which lack a pacemaker, the effects of orciprenaline sulphate and isoproterenol are similar whereas when a pacemaker is present, as in the right atrium, the effect of orciprenaline sulphate is much less than that of isoproterenol. It can be concluded that orciprenaline sulphate, like isoproterenol, acts mainly on the sinus node in the right atrium and that the affinity of orciprenaline sulphate for the pacemaker is appreciably less than that of isoproterenol. In heart preparations which ordinarily do not beat spontaneously, orciprenaline sulphate induced spontaneous activity much less frequently than isoproterenol. In guinea–pigs, doses of orciprenaline sulphate from 1 to 100 mg/kg intravenously failed to induce any cardiac arrhythmia. On the other hand, orciprenaline sulphate provided protection against arrhythmias experimentally induced by adrenaline. For example, 30 minutes to 2 hours after 30-100 mg/kg of orciprenaline sulphate had been administered intravenously, arrhythmias were not induced by doses of adrenaline from 3 to 30 times greater than those which formerly produced arrhythmias.

Effects on Other Systems

Orciprenaline sulphate produces an inhibitory effect on the smooth muscle of the gastrointestinal tract, as demonstrated by its action on histamine and acetylcholine–induced contractions of the isolated guinea–pig ileum and on serotonin–induced spasm of the rat duodenum. The inhibitory effect on the gastrointestinal tract was further demonstrated by studying charcoal meal progression in the guinea–pig.

A mild mydriatic effect has been shown in mice and on the enucleated eyes of cattle.

Metabolism

Excretion studies in humans with the orally administered labelled compound have demonstrated that an average of approximately 40% of the drug is absorbed. The drug is excreted primarily as glucuronic acid conjugates. Animal studies (rat, rabbit and monkey) have also demonstrated good absorption as evidenced by recovery of substantial amounts in the urine. The major metabolite in animals is also the conjugated form of the drug. The concentration of radioactivity in blood plasma was determined in rabbits following intravenous administration of radiolabelled orciprenaline sulphate. Radioactivity decreased in two phases of different velocity. During the first phase, the decrease is linear on the semilogarithmic scale with a half–life of about 40 minutes. This may represent tissue penetration. The second phase is considerably slower and has a half–life of approximately 15 hours.

TOXICOLOGY

The toxic effects of orciprenaline sulphate have been studies in 5 species: rat, mouse, rabbit, dog and monkey. In acute and subchronic studies, orciprenaline sulphate was given by various routes including oral, inhalation, intravenous, intraperitoneal, and subcutaneous and in doses ranging from 0.2 mg to 500 mg/kg.

Acute Toxicity

The following table compares the LD_{50}'s in various species for oral orciprenaline sulphate.

Species	LD_{50} (mg/kg)
Rat	4420-5276
Mouse	4800-8130
Rabbit	3114-5000
Dog	50-900
Monkey	4000

The oral LD_{50} ranges represent values found by different investigators.

In mice, for an oral LD_{50} of 4800 mg/kg, the subcutaneous LD_{50} is 200 mg/kg and the intravenous LD_{50} is 114 mg/kg. Depending upon the species and the dosage, the toxic signs included decreased activity followed by hyperpnea and salivation, which proceeded to ataxia, and finally, prostration or convulsions before death. Animals which survived the toxic dose had uneventful recoveries.

Subchronic Toxicity

Orciprenaline sulphate has been studied for various periods in rats, dogs and monkeys. In rats given up to 25 times (4.5, 13.5, 40.5 mg/kg/day) the recommended maximum human dose orally for 3 months, there were only increases in the weights of the hearts and livers. In dogs given orciprenaline sulphate for 3 months in doses of 6.25, 25 and 100 mg/kg/day, there were no dose–related toxic effects, although one dog in each of the three drug level groups died following the first dose. In monkeys, doses of orciprenaline sulphate of 10, 30 and 100 mg/kg/day for six months had no demonstrable toxic effects and all the animals survived.

Inhalation Toxicity

Hemorrhages occurred in the myocardium and bladder mucosa of 2 of 6 dogs that received 0.5-0.6 mg of orciprenaline sulphate aerosol/kg/day for 3 months. Three of 6 dogs that received a single dose of 11 to 13 mg of drug per kg had endocardial and/or renal hemorrhages; one of

these also had a small hemorrhage in the circle of Willis. Petechial hemorrhages were observed in the coronary groove and auricles of a dog that died, and suspicious macroscopic lesions occurred in the hearts of 6 other dogs that received doses of orciprenaline sulphate aerosol ranging from 125 to 455 mg/kg.

Questionable macroscopic lesions also occurred in kidneys and hearts of monkeys given 250-750 mg/kg. However, isoproterenol also causes myocardial hemorrhages and infarcts in dogs and rats. Subcutaneous doses as small as 2.5 and 0.8 mg/kg produced these effects in dogs and rats respectively; minimal hemorrhage–producing doses were not investigated in the canine experiment.

Teratogenicity

The teratogenicity of orciprenaline sulphate has been studied in rabbits, rats, mice and monkeys. In rabbits and rats, the drug was given orally and parenterally; in mice it was given only parenterally; in monkeys it was given only orally. The results of these studies indicate that orciprenaline sulphate has no appreciable teratogenic effects even at dosages considerably higher than the recommended human dose. At extremely high dosage levels in the rabbit, all sympathomimetic amines studied (ephedrine, isoproterenol, orciprenaline sulphate, and phenylephrine) caused abnormalities such as limb flexures, agenesis of digits, hydrocephalus, agenesis of mouth, cleft palate and polycystic liver, in a proportion of the test animals. At the high dosage levels used in these studies, there was a decreased conception rate suggesting maternal toxicity. There was also suggestive evidence that the pregnant rabbit was more susceptible to the toxic effects which occur at extremely high dosage levels, than non–pregnant animals.

BIBLIOGRAPHY

1. Aepli R. Bronchospasmolytic activity of isoproterenol (Aleudrin®) and orciprenaline (Alupent®) aerosol. Helv Med Acta 1965; 32: 511.

2. Betancourt VM, Mendez S. The bronchodilating activity of Alupent®. XI Congr Mac de Neumol y Cir de Torax Torreon Coah 1965; 13-17.

3. Beumer HM. Bronchospasm on the basis of allergy and antagonistic substances. Les Bronches 1964; 14: 440.

4. Beynon-Jones DC. A clinical trial of Alupent®, a new bronchodilator, in general practice. Brit J Clin Pract 1962; 16: 803.

5. Bilodeau M, Roy JC. Ventilation studies for the evaluation of bronchodilator aerosols: Comparative study of isoproterenol and metaproterenol sulphate. Canad Med Assoc J 1968; 99: 585.

6. Drewitt AH. First clinical experiences with Alupent® - a new bronchodilator. Brit J Clin Pract 1962; 16: 549.

7. Edwards G. Orciprenaline in treatment of airways obstruction in chronic bronchitis. Brit Med J 1964; 5389: 1015.

8. Engelhardt A, et al. Pharmacology of the sympathomimetic amimetic amine drug 1-(3,5-dihydroxyphenyl)-1 hydroxy-2-isopropyl-aminoethane. Drugs made in Germany 1961; 4: 123.

9. Feinsilver O. Airway resistance as an index of effectiveness of bronchodilating drugs. J Allergy 1966; 38: 195.

10. Garay Lillo J, et al. Clinical statistical evaluation of the bronchodilating activity of a form of Alupent® in measured dose manual aerosol compared with conventional aerosolization of the same drug. Much Med Wschr Ed Esp 1966; 108: 517.

11. Holmes TH, Morgan B. A comparative clinical trial of metaproterenol and isoproterenol as bronchodilator aerosols. Clin Pharmacol Ther 1968; 9: 615.

12. Ieda M. Long–term therapy with Alotec®. The Treatment 1965; 18: 696.

13. Ishikawa S, Cherniak RM. The effect of nebulized bronchodilators on air flow resistance in chronic airways obstruction. Am Rev Resp Dis 1969; 99: 703.

14. Kennedy MCS. A new bronchodilator drug: Alupent® (TH 152). Brit J Clin Pract 1963; 17: 563.

15. Kennedy MCS, Jackson SLO. Oral sympathomimetic amines in treatment of asthma. Brit Med J 1963; 5371: 1506.

16. Kessler F. Clinical trial of metaproterenol aerosol in bronchial asthma. Ann Allergy 1964; 22: 588.

17. Martini M, Conti F. Clinical application of a new antiasthmatic drug (Th 152) in aerosol form. Osped Maggiore 1964; 59: 388.

18. Meier J, Lydtin H, Zoellner N. The effect of adrenergic beta receptor blocking agents on ventilatory function in obstructive pulmonary diseases. Dtsch Med Wschr 1966; 91: 145.

19. Miller WF, et al. Functional responses to bronchodilator aerosols in asthma, bronchitis and emphysema. Cong Proc Interasma V Utrecht May 1966 Amer Drug 1967; 155: 49.

20. Morton WJ, et al. A comparative study of aerosol, oral and intravenous administration of bronchodilators in asthma, with the use of isoproterenol (Isuprel®), TH 152 and aminophylline. J Allergy 1963; 34: 16.

21. Rebuck AS, Read J. Oral orciprenaline in the treatment of chronic asthma. Med J Aust 1969; 1: 445.

22. Rona G, Chapel C, Balazs T, Gaudry R. An infarct–like myocardial lesion and other toxic manifestations produced by isoproterenol in the rat. AMA Arch Path 1959; 67: 443.

23. Rona G, Zsoter T, Chapel C, Gaudry R. Myocardial lesions circulatory and electrocardiographic changes produced by isoproterenol in the dog. Rev Canadienne Bio 1959; 18: 83.

24. Shanks RG, et al. Stimulation of adrenergic β–receptors by orciprenaline. Brit Med J 1967; 1: 610.

25. Simon SW, Lipman WH. Metaproterenol - a new bronchodilating drug. Ann Allergy 1963; 21: 260.

26. Sinclair JD. The response of asthmatics to bronchodilator aerosols. New Zealand Med J 1966; 65: 524.

27. Svanborg N. Comparison between effects of some aerosols with anti-asthmatic effects on the airflow in asthma and emphysema. Acta Allergologica 1964; XIX: 316.

28. Woolcock AJ. Assessment of orciprenaline (Alupent®), a long–acting bronchodilator. The Med J Australia. 1964.

29. Editorial: Adrenaline and isoprenaline in myocardial failure. Lancet 1965; 2: 122