NAME OF MEDICINE

The name of the medicine is Phenoxybenzamine hydrochloride [(RS)-benzyl(2-chloroethyl)-1-methyl-2-phenoxyethylamine hydrochloride].

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\text{Formula: } \text{C}_{18}\text{H}_{22}\text{ClNO.HCl}
\]

CAS No: 63-92-3

DESCRIPTION

Phenoxybenzamine hydrochloride is a white or almost white, crystalline powder. Phenoxybenzamine hydrochloride is a long acting, adrenergic $\alpha$-receptor blocking agent. Phenoxybenzamine hydrochloride is sparingly soluble in water, freely soluble in chloroform and ethanol (96%).

Formula: C\textsubscript{18}H\textsubscript{22}ClNO.HCl

MW: 340.3

PHARMACOLOGY

Phenoxybenzamine does not block beta-adrenoceptors. It increases blood flow to the skin, mucosa and abdominal viscera and lowers both supine and erect blood pressures. It has no effect on the parasympathetic system.

Phenoxybenzamine prevents the uptake of amines into neuronal and extraneuronal storage sites thereby potentiating the action of noradrenaline and adrenaline on beta-receptors. It also causes non-competitive blockade of receptors for histamine, serotonin, and acetylcholine (muscarinic). Phenoxybenzamine is thought to exert its pharmacological action as an alkylating agent. Pharmacological effects of particular relevance for the approved indications and in the recommended dose range are:
i. long-lasting blockade of vascular alpha-adrenoreceptors with resulting decrease in peripheral resistance and, in phaeochromocytoma, prevention of paroxysmal hypertension due to high levels of circulating catecholamines;

ii. blockade of alpha-adrenoreceptors on the distal urethral sphincter and smooth muscle of the bladder neck, thereby reducing bladder outflow resistance.

However, other autonomic and reflex effects predictable from the above pharmacological actions may occur in clinical use.

Twenty to thirty percent of orally administered phenoxybenzamine appears to be absorbed in the active form. The half-life of orally administered phenoxybenzamine hydrochloride is not known; however, the half-life of intravenously administered drug is approximately 24 hours.

Demonstrable effects with intravenous administration persist at least three to four days, and the effects of daily administration are cumulative for nearly a week.

INDICATIONS
Hypertensive episodes associated with phaeochromocytoma. Treatment of urinary retention due to neuropathic bladder.

CONTRAINDICATIONS
Conditions where a fall in blood pressure is undesirable such as cerebrovascular accidents and in the recovery period following acute myocardial infarction.

Warning
Dibenzyline-induced α-adrenergic blockade leaves β-adrenergic receptors unopposed. Compounds that stimulate both types of receptors may therefore produce an exaggerated hypotensive response and tachycardia.

PRECAUTIONS

Mutagenicity and Carcinogenicity
Phenoxybenzamine hydrochloride has shown *in vitro* mutagenic activity in the Ames bacterial salmonella assay and in the mammalian (mouse) lymphoma cell assay. No mutagenic activity was detected in the micronuclease test in mice.

Carcinogenicity studies showed phenoxybenzamine to be positive in four bioassays. These were an increased incidence of pulmonary tumours in strain A mice over 24 weeks, increased incidences of peritoneal sarcomas in rats and mice following intraperitoneal administration, and increased incidences of squamous cell carcinomas of the non-glandular stomach and sarcomas and carcinomas of the jejunum in rats following chronic oral administration.

In chronic oral studies in rats, ulcerative and/or erosive gastritis of the glandular stomach occurred which was probably drug related.

The clinical significance of these results is not established but they should be given due consideration in determining the benefit-risk ratio as it applies to the individual patient particularly in the younger age group. It is also recommended that treatment duration be kept as short as possible.

Dibenyl line should be administered with caution in patients with marked cerebral or coronary arteriosclerosis or renal damage and in patients where tachycardia or hypotension would be undesirable. Adrenergic blocking effect may aggravate symptoms of respiratory infections.

**Use in Pregnancy**
Adequate human and animal data on use during pregnancy are not available. Dibenyl line should be given to a pregnant woman only if clearly needed.

**Use in Lactation**
Adequate human and animal data on use during lactation are not available. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from phenoxybenzamine 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.

**Paediatric Use**
Safety and effectiveness in children have not been established.
**DRUG INTERACTIONS**

Phenoxybenzamine may interact with compounds that stimulate both α- and β-adrenergic receptors (i.e. adrenaline) to produce an exaggerated hypotensive response and tachycardia (see **Warnings**). Phenoxybenzamine blocks hyperthermia production by noradrenaline and blocks hypothermia production by reserpine.

**ADVERSE EFFECTS**

**Autonomic Nervous System**

Nasal congestion, miosis, postural hypotension with dizziness and compensatory tachycardia, inhibition of ejaculation. These effects may decrease as therapy continues.

**General**

Gastrointestinal irritation, drowsiness and fatigue have also been reported.

**DOSAGE AND ADMINISTRATION**

**Adults**

**In Phaeochromocytoma**- the dosage generally required to achieve blood pressure control is 1 - 2 mg/kg body weight daily.

Small initial doses (10 mg twice a day) should be slowly increased until the desired effect is obtained or the adverse reactions from blockade become troublesome. The patient's response should be your guide after each increase, the patient should be observed at that level for at least four days before instituting another increase. Dosage range is usually 20 to 60 mg daily in two doses.

Concomitant beta-adrenergic blockage may be necessary to control tachycardia and arrhythmias when phaeochromocytomas are excreting an appreciable amount of adrenaline as well as noradrenaline.

In **urinary retention** due to **neurogenic bladder**, 10mg twice a day is usually sufficient. If no effect is seen in 2 to 3 weeks, alternative therapy should be used.

**OVERDOSAGE**

**Symptoms**

The symptoms are largely the result of a block of the sympathetic nervous system and of circulating adrenaline. They may include postural hypotension, resulting in dizziness or fainting; tachycardia, particularly postural; vomiting; lethargy; shock.
**Treatment**

Treatment of circulatory failure, if present, is a prime consideration. In cases of mild overdosage, recumbent position with legs elevated usually restores cerebral circulation. In the more severe cases, the usual measures to combat shock should be instituted. Usual pressor agents are not effective. Adrenaline is contraindicated because it stimulates both alpha and beta receptors. Since $\alpha$-adrenoreceptors are blocked, the net effect of adrenaline administration is vasodilation and a further drop in blood pressure (adrenaline reversal).

The patient may have to be kept recumbent for 24 hours or more in the case of overdose, as the effect is prolonged. Leg bandages and an abdominal binder may shorten the period of disability.

Intravenous infusion of noradrenaline may be used to combat severe hypotensive reactions because it stimulates alpha receptors primarily. Although phenoxybenzamine is an alpha adrenergic blocking agent, a sufficient dose of noradrenaline will overcome this effect.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

**PRESENTATION AND STORAGE CONDITIONS**

Red/white capsules marked *Dibenyline* containing phenoxybenzamine hydrochloride 10 mg, packs of 100 in HDPE containers. Store below 30°C.

Also contains: purified talc, lactose, erythrosine, indigo carmine, titanium dioxide and gelatin.

**NAME AND ADDRESS OF SPONSOR**

Goldshield Healthcare (Australia) Pty Ltd
Suites 3, Level 1
118-124 Willoughby Road,
CROWS NEST NSW 2065

**POISON SCHEDULE OF THE MEDICINE**

Schedule 4.

Date of approval: September 18, 1990.
Safety-related notification: February 16th 1999
Date of last amendment: 1st September, 2006