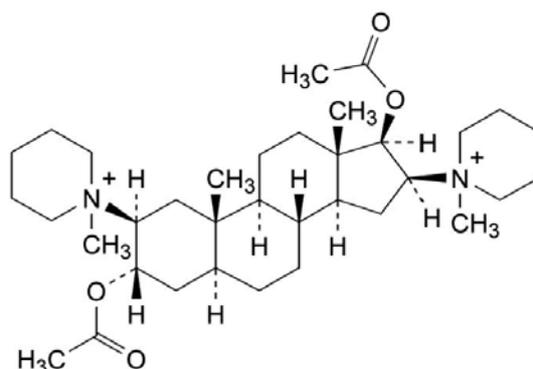


Pancuronium Injection BP
Pancuronium Bromide 2 mg/mL
PRODUCT INFORMATION

NAME OF THE DRUG

The Australian Approved Name is pancuronium bromide (molecular formula $C_{35}H_{60}Br_2N_2O_4$). The chemical name for pancuronium bromide is 2 β ,16 β -dipiperidino-5 α -androstane-3 α ,17 β -diol diacetate dimethobromide. The CAS number for pancuronium bromide is 15500-66-0.

Chemical structure:



DESCRIPTION

A sterile solution of pancuronium bromide suitable for IV injection. Each 2 mL ampoule contains pancuronium bromide 4 mg, sodium acetate 4 mg, sodium chloride 6 mg in Water for Injections BP; pH 3.5 - 4.2.

PHARMACOLOGY

Pancuronium bromide is a nondepolarising neuromuscular blocking agent of medium duration, blocking transmission of motor nerve impulses to striated muscle receptors, producing skeletal muscle paralysis. It competes with acetylcholine for cholinergic receptor sites. It has little agonist activity, having no depolarising effect at the motor endplate. Skeletal muscle relaxation starts with muscles associated with fine movements, e.g. eyes, face and neck, then followed by muscles of the limbs, chest, abdomen and finally the diaphragm. Larger doses increase the risk of respiratory depression due to relaxation of the intercostal muscle and diaphragm. Muscle tone returns in the reverse order. Pancuronium bromide also increases heart rate by a direct blocking effect on acetylcholine receptors in the heart, but this effect is small with therapeutic doses. It produces little or no significant ganglion blockade, so hypotension and bronchospasm are not associated with its use. The muscle weight-to-body weight ratio, the volume of extracellular fluid and renal function also contribute to response.

Despite its steroid structure, pancuronium bromide exhibits no hormonal activity. Cholinesterase inhibitors such as pyridostigmine and neostigmine reverse the action of pancuronium.

Pharmacokinetics

With an initial dose of pancuronium bromide of 0.06 mg/kg IV, muscle relaxation reaches a level suitable for endotracheal intubation within 2 to 3 minutes, and the effects of the drug begin to subside in about 35 to 45 minutes (these data are approximations since muscle relaxant response may be variable).

Onset and duration of action of pancuronium bromide is dose dependent. Supplemental incremental doses, following the initial dose, slightly increase the magnitude of blockade, and significantly increase the duration of blockade alone or following suxamethonium.

Following intravenous injection pancuronium bromide is rapidly distributed into body tissues. Figures of 30 - 87% protein binding have been reported. Small amounts of pancuronium bromide cross the placenta.

Plasma concentrations appear to fall in a triphasic manner, the last phase having a half-life of about 2 hours. Metabolism occurs via hepatic pathways to at least 3 metabolites, a 3-hydroxy metabolite, a 17-hydroxy metabolite and a 3,17-hydroxy metabolite. These metabolites are significantly less potent than pancuronium. Most of the drug and its metabolites are excreted in the urine. About 80% is excreted in the urine and 10% in the faeces as unchanged pancuronium. A small amount is excreted in the bile.

Since a large fraction of pancuronium bromide is excreted in the urine, the duration of neuromuscular blockade is prolonged in patients with renal failure and the dose should be reduced. In patients with impaired hepatic function, prolonged distribution and elimination half-lives result in a higher initial dose to be given and longer duration of action respectively.

INDICATIONS

1. An adjunct to surgical anaesthesia to induce skeletal muscle relaxation to facilitate operative manipulations. The necessary conditions for intubation can be achieved with pancuronium bromide alone or following suxamethonium.
2. Pancuronium bromide is also indicated to promote mechanical ventilation by reducing or eliminating spontaneous breathing effort in intensive care patients.

CONTRAINDICATIONS

Known hypersensitivity to pancuronium bromide or to the bromide ion.

PRECAUTIONS

General

Pancuronium bromide should only be used in hospitals equipped with suitable equipment for anaesthesia and/or resuscitation with reversal agents immediately available and administered only by a qualified anaesthetist or a physician experienced in anaesthetics. All patients receiving pancuronium bromide should be intubated and given artificial respiration until spontaneous respiration returns.

Electrolyte imbalance, altered pH and dehydration should be corrected if possible before the administration of pancuronium bromide. Electrolyte imbalance (hypokalaemia, hyponatraemia, hypermagnesaemia, hypocalcaemia), acid/base imbalance (respiratory acidosis or metabolic alkalosis), dehydration, hypoproteinaemia and cachexia can increase the neuro-muscular blocking activity of pancuronium bromide. In burned patients, resistance to the neuromuscular blocking action of pancuronium bromide may be encountered as with other nondepolarising relaxants. In addition, pancuronium bromide should be used cautiously in patients with conditions that may lead to electrolyte imbalances such as adrenal insufficiency.

Prior administration of suxamethonium has been reported to increase the intensity and duration of neuromuscular blockade produced by pancuronium bromide and a reduction in pancuronium bromide dosage is recommended. Administration of depolarising drugs such as suxamethonium following pancuronium bromide is not recommended.

Do not mix pancuronium bromide with other solutions in the same syringe as a change in the pH may induce precipitation.

Care should be exercised if there is a danger of regurgitation when intubating the patient, for example during crash induction.

Pancuronium bromide is antagonised by acetylcholine, anticholinesterases and potassium ions. The action of pancuronium bromide may also be altered by concomitant administration of various drugs such as neuromuscular blocking agents, some antibiotics and certain anaesthetics (see **Interactions with other drugs**).

Hypersensitivity reactions

Anaphylactic reactions to neuromuscular blocking agents in general have been reported. Although these are very rarely seen with pancuronium bromide, precautions for treating such reactions if they would occur should always be taken. Particularly in the case of known former anaphylactic reactions to neuromuscular blocking agents, special caution should be taken since allergic cross reactivity between neuromuscular blocking agents has been reported.

Since neuromuscular blocking agents in general are known to be capable of inducing histamine release both locally at the site of injection and systemically after intravenous injection, the possible occurrence of itching and erythematous reactions at the site of injection and/or generalised histaminoid (anaphylactoid) reactions should always be taken into consideration when administering pancuronium bromide.

Neuromuscular Syndromes

Extreme caution should be exercised and reductions in dosage made when administering pancuronium bromide to patients with myasthenia gravis, myasthenic syndrome associated with small cell carcinomatosis (Eaton-Lambert syndrome; originally associated with lung cancer), prior poliomyelitis or myopathy or any other neuromuscular disease (such as amyotrophic lateral sclerosis) as small doses may have profound effects.

Obesity

In severe obesity, pancuronium bromide should be used with extreme caution and dosed carefully since the volume of distribution for muscle relaxants is approximately equivalent to that of extracellular volume. It is important to dose obese patients based on their lean body weight to prevent intense block of long duration and possible overdose. In addition, patients with severe obesity may be predisposed to airway or ventilatory problems which require special care before, during and after treatment with pancuronium bromide (see Precautions - respiratory disorders).

Cardiovascular Disorders

Pancuronium bromide should not be used in patients with pre-existing tachycardia or in patients in whom even a minor elevation in heart rate is undesirable as pancuronium bromide increases the heart rate by direct action on the acetylcholine receptors in the heart. Pancuronium bromide should be used with caution in patients with a tendency to hypertension including hypertension associated with phaeochromocytoma or renal disease since increases in arterial pressure may be observed with pancuronium bromide, due to vagolytic effects and secondarily by blocking the neuronal reuptake of noradrenaline.

Prolonged therapy

Individual cases of prolonged paralysis, disuse atrophy and areflexia have been reported in association with prolonged use of pancuronium bromide to assist mechanical ventilation. It is unclear whether the motor dysfunction was due to the duration of neurological blockade (usually greater than 7 days), prolonged bedrest, underlying clinical condition, intervention of synergistic drugs or a combination of such factors. Improvement was seen after 2 - 5 months in some but not all cases.

Careful monitoring of motor function is therefore particularly important when prolonged pancuronium bromide-induced neurological blockade is necessary.

Hypothermia/Hyperthermia

Hypothermia reduces the intensity of neuromuscular blockage and increased doses of pancuronium bromide may be required. Hyperthermia has the opposite effect. When hypothermia techniques are used during surgery, the reduction in neuromuscular blockade is reversed when the patient is rewarmed.

Ophthalmic

Pancuronium bromide has been reported to produce a significant (+/- 20%) fall in normal and elevated intraocular pressure for some minutes following administration and also to produce miosis. These changes may attenuate the rise in intraocular pressure due to laryngoscopy and endotracheal intubation.

Respiratory disorders

Neuromuscular blocking agents can cause respiratory paralysis as a result of respiratory depression and should be used with extreme caution in patients with pulmonary disease such as chronic obstructive pulmonary disease (COPD).

Carcinomas

Patients with carcinomatosis especially associated with bronchial carcinoma may exhibit a marked sensitivity to pancuronium bromide, and the neuromuscular block produced may respond poorly to neostigmine.

Malignant hyperthermia

Patients with a familial history of malignant hyperthermia should be treated with extreme caution. The condition can be precipitated by the use of halogenated anaesthetics because this reaction has been attributed to their use, but neuromuscular blocking agents also may be a contributory factor.

Use in hepatic impairment

Pancuronium bromide should be used with caution in patients with hepatic impairment. The elimination half-life is doubled in patients with biliary obstruction or cirrhosis and plasma clearance is decreased by <50% or about 22% respectively. In addition, patients with hepatic disease may have a 50% increase in the volume of distribution of pancuronium bromide. This usually results in the need for a higher initial dose to achieve adequate muscle relaxation and a prolonged duration of action.

Use in renal impairment

As pancuronium bromide is excreted mainly in the renal system, the elimination half-life is prolonged in patients with poor renal perfusion or renal disease, resulting in a reduction in plasma clearance and prolonged duration of action. Reduction of maintenance doses may be necessary. Pancuronium bromide should be avoided in patients with a GFR of less than 10 mL per minute; recurarisation might occur up to 24 hours after administration.

Use in neonates

Neonates are particularly sensitive to pancuronium bromide and nondepolarising neuromuscular blocking agents in general. Dosage must be individualised (see **Dosage and Administration**) and further reductions may be necessary in prematurity, acidosis, hypothermia and during antibiotic therapy.

Use in elderly

Plasma concentrations have been reported to decline at a decreased rate in the elderly however dosage reduction is not indicated.

However, elderly patients are more likely to have age-related renal function impairment, which may decrease the rate of clearance of pancuronium bromide and thereby prolong its effect.

Use in pregnancy Category B2

The safe use of pancuronium bromide has not been established with respect to possible adverse effects upon foetal development. Therefore, it should not be used in women in pregnancy or those likely to become pregnant unless the potential benefits outweigh the unknown hazards.

Pancuronium bromide may be used in operative obstetrics (caesarean section) but reversal of drug effects may be unsatisfactory in patients receiving magnesium sulphate for toxæmia of pregnancy. Magnesium salts enhance neuromuscular blockade and therefore a reduced dosage of pancuronium bromide is indicated.

Pancuronium bromide has been found to cross the placenta in small amounts

Interactions with other drugs***Anaesthetics***

Certain anaesthetic agents may influence the neuromuscular blocking activity of pancuronium bromide. Halothane, ether, enflurane, isoflurane, methoxyflurane, thiopentone, methohexitone, ketamine and fentanyl, may increase neuromuscular blocking activity while neuroleptanalgesia may decrease activity.

Other Drugs

Concomitant neomycin, streptomycin, kanamycin, gentamicin, bacitracin, polymyxins, tetracyclines, diazepam, propranolol, thiamine (high dose), IV lignocaine (high dose), magnesium sulphate, lithium carbonate, monoamine oxidase inhibitors, quinine, quinidine, protamine, diuretics, phenytoin, alpha-adrenergic blocking agents, beta-adrenergic blocking agents, calcium channel blockers, imidazoles, metronidazole and magnesium salts, magnesium ions and large infusions of citrate-anticoagulated blood may potentiate the neuromuscular blocking effects of pancuronium bromide.

Neostigmine, edrophonium, pyridostigmine, high dose corticosteroid, adrenaline, azathioprine, theophylline (high dose), potassium chloride, sodium chloride and calcium chloride may decrease the activity of pancuronium bromide.

Prior administration of suxamethonium can increase the intensity of neuromuscular blockage due to pancuronium bromide (see **Precautions** and **Dosage and Administration**).

Pancuronium bromide can antagonise the effects of antimuscarinics. Temporary dosage adjustment following surgery may be necessary (see **Precautions - Neuromuscular syndromes**).

Calcium salts usually reverse the effects of pancuronium bromide.

Hypokalaemia potentiates neuromuscular blockade with nondepolarising neuromuscular blockers. Drugs which are associated with a significant risk of hypokalaemia (e.g. amphotericin B, cisplatin, corticosteroids, loop diuretics, thiazide diuretics) should be monitored closely when used with pancuronium bromide.

Hydrocortisone and prednisone can decrease the effect of pancuronium bromide, necessitating either increased doses of pancuronium bromide or substitution of another nondepolarising neuromuscular blocker.

The effects of botulinum toxin type A or B can be potentiated by pancuronium bromide or other drugs that interfere with neuromuscular transmission.

Pancuronium bromide increases the risk of developing arrhythmias and should be used with caution in patients receiving cardiac glycosides.

Caution is indicated when piperacillin is used perioperatively as the neuromuscular blockade produced by pancuronium bromide could be prolonged in the presence of piperacillin.

Injection compatibilities

See **Dosage and Administration**

ADVERSE REACTIONS

Respiratory

Complications are rare and usually associated with overdose. This may result in prolonged apnoea or respiratory depression.

Cardiovascular

After administration approximately 10% of patients may exhibit mild to moderate increases in blood pressure and/or pulse rate. Dysrhythmias may occasionally occur and increased cardiac output is frequently noted.

Hypersensitivity

Hypersensitivity reactions occur rarely. Bradycardia, bronchospasm, hypotension and cardiovascular collapse have been reported. An occasional transient rash has been reported. Pruritus can occur, as well as rare cases of flushing, oedema and wheezing.

Skin and Appendages

A few cases of local reactions manifested by pain and burning at the site of injection have been reported.

Ocular

Pancuronium bromide decreases intraocular pressure and induces miosis.

Neuromuscular

As with all muscle relaxants, abnormal reactions may be seen in patients with neuromuscular diseases. Prolonged paralysis, disuse atrophy and areflexia have been reported with prolonged use of pancuronium bromide (see Precautions).

Other

Hypersalivation following pancuronium bromide administration may occur, especially if no anticholinergic premedication is given.

DOSAGE AND ADMINISTRATION

The following dosage information is a guide only.

Pancuronium bromide is given by intravenous administration. The dosage should be individualised for each patient as there is wide variation in individual response to muscle relaxants. The potential effect of the anaesthetic or any other concomitant drug, clinical state of the patient and the anticipated duration of the neuromuscular block must be taken into account when the dosage is determined.

It is recommended that a peripheral nerve stimulator be used to monitor response to pancuronium bromide to minimise the risk of overdosage.

Since potent inhalation agents or prior administration of suxamethonium enhance the intensity of blockade and duration of action of pancuronium bromide, these factors should be considered when selecting initial and incremental dosage.

In heavy or obese patients doses of pancuronium based on mg/kg may lead to overdosage.

For use in one patient on one occasion only. Discard any unused contents of an opened ampoule.

Adults: (Aged 12 years and above)

Initial and incremental doses: Initial dose range is 0.04 to 0.15 mg/kg depending on surgical procedure. Incremental doses 0.01 to 0.02 mg/kg.

For endotracheal intubation when pancuronium is given in a dose range of 0.05 to 0.15 mg/kg conditions satisfactory for intubation are usually present within 2 to 3 minutes.

Maintenance dose: Additional doses of 0.01 mg/kg may be administered at 25 to 60 minute intervals to maintain skeletal muscle relaxation during prolonged surgery. Doses of 0.015 mg/kg may be used to maintain relaxation for controlled respiration.

Children: (Aged 1 month to 12 years)

Initial and incremental doses: 0.06 to 0.08 mg/kg initially intravenously followed by increments of 0.01 to 0.02 mg/kg thereafter.

Maintenance dose: Additional doses of 0.01 mg/kg may be administered at 25 to 60 minute intervals to maintain skeletal muscle relaxation during prolonged surgery. Doses of 0.015 mg/kg may be used to maintain relaxation for controlled respiration.

Neonates:

Dosage of pancuronium bromide in neonates up to one month of age must be carefully individualised, since neonates are particularly sensitive to non-depolarising neuromuscular blocking agents.

Dosage: 0.03 to 0.04 mg/kg intravenously initially followed by increments of 0.015 to 0.02 mg/kg thereafter.

An initial test dose of 0.02 mg/kg has been suggested to determine responsiveness.

After suxamethonium for intubation:

A reduction in the initial dose of pancuronium bromide is recommended when it is given following administration of suxamethonium. For adults and children older than 1 month, the initial dose should be reduced by approximately one third to 0.02 to 0.06 mg/kg and the incremental doses should be 25 to 33% of the initial dose.

Elderly:

Plasma concentrations have been reported to decline at a decreased rate in the elderly. The dosage should be adjusted with caution and lower doses may be required.

Impaired hepatic function:

In patients with impaired hepatic function (eg cirrhosis of the liver) the distribution half-life and elimination half-life are significantly prolonged. Thus, the initial dose of pancuronium bromide necessary to achieve effective muscle relaxation is increased and the rate of disappearance from the plasma is slower.

Impaired renal function:

The effect of pancuronium bromide may be prolonged as the drug is excreted predominantly unchanged in the urine; therefore, a reduction in the maintenance dose may be necessary. Pancuronium bromide should be avoided in patients with a glomerular filtration rate (GFR) of less than 10 mL per minute; re-occurarisation might occur up to 24 hours after administration.

Use in intensive care patients:

The action of pancuronium bromide may be enhanced in the intensive care patient requiring assisted ventilation. Dosages should be titrated according to clinical response and peripheral nerve stimulation monitoring. It is recommended to commence dosing for this group of patients at the lower end of the dosage range. ie. 0.04 mg/kg for adults.

Injection Incompatibilities

Do not mix other solutions in the same syringe as a change in pH may cause precipitation. A precipitate may form if pancuronium bromide is mixed with barbituates in the same syringe.

Pancuronium bromide is stable for up to 48 hours in the following infusion solutions: 5% glucose, 0.9% sodium chloride, lactated Ringer's, or 5% glucose and 0.45 or 0.9% sodium chloride. However, for microbiological reasons, diluted solutions should be used as soon as practicable. If storage is necessary, diluted solutions should be stored at 2 - 8°C and used within 24 hours of dilution.

OVERDOSAGE

Symptoms

Symptoms of overdose are prolonged apnoea, respiratory depression, persistent muscle weakness, significant hypotension and shock. Death may follow acute respiratory failure.

Treatment

The patient should remain under artificial respiration with intermittent positive pressure ventilation. At the same time the neuromuscular action of pancuronium bromide may be reversed by the administration of atropine and neostigmine at incremental doses within the prescribed therapeutic range and assisted ventilation should continue until recovery is complete.

PRESENTATION

Polyamp DuoFit[®]: 4 mg/2 mL; 50s.

STORAGE

Store at 2-8°C until use. DO NOT FREEZE.

Pancuronium need not be refrigerated during normal periods of use in theatres.

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine)

NAME AND ADDRESS OF THE SPONSOR

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Polyamp Duofit is a trade mark of the AstraZeneca group of companies.

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