PRESCRIBING INFORMATION

PANCURONIUM BROMIDE INJECTION

ABBOTT Standard

1 mg/mL Vials and 2 mg/mL Ampoules

Nondepolarizing Neuromuscular Blocking Agent

Hospira Healthcare Corporation
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H4M 2X6

Control#: 162429

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THERAPEUTIC CLASSIFICATION

Nondepolarizing Neuromuscular Blocking Agent

ACTION AND CLINICAL PHARMACOLOGY

PANCURONIUM BROMIDE INJECTION is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by anticholinesterase agents such as pyridostigmine, neostigmine, and edrophonium. Pancuronium is approximately 1/3 less potent than vecuronium and approximately 5 times as potent as d-tubocurarine: the duration of neuromuscular blockade produced by pancuronium is longer than that of vecuronium at initially equipotent doses.

The onset and duration of action of pancuronium are dose-dependent. The ED_{95} (dose required to produce 95% suppression of muscle twitch response) is approximately 0.05 mg/kg under balanced anesthesia and 0.03 mg/kg under halothane anesthesia.

These doses produce effective skeletal muscle relaxation (as judged by time from maximum effect to 25% recovery of control twitch height) for approximately 22 minutes: the duration from injection to 90% recovery of control twitch height is approximately 65 minutes. The intubating dose of 0.1 mg/kg (balanced anesthesia) will effectively abolish twitch response within approximately 4 minutes: time from injection to 25% recovery from this dose is approximately 100 minutes.

Supplemental doses to maintain muscle relaxation slightly increase the magnitude of block and significantly increase the duration of block.

The most characteristic circulatory effects of pancuronium, studied under halothane anesthesia, are a moderate rise in heart rate, mean arterial pressure and cardiac output: systemic vascular resistance is not changed significantly and central venous pressure may fall slightly. The heart rate rise is inversely related to the rate immediately before administration of pancuronium, is blocked by prior administration of atropine, and appears unrelated to the concentration of halothane or dose of pancuronium.

Pharmacokinetics:

The elimination half-life of pancuronium has been reported to range between 89 to 161 minutes. The volume of distribution ranges from 241 to 280 mL/kg and plasma clearance is approximately 1.1 to 1.9 mL/minute/kg. Approximately 40% of the total dose of pancuronium has been recovered in urine as unchanged pancuronium and its metabolites while approximately 11% has been recovered in bile.

As much as 25% of an injected dose may be recovered as 3-hydroxy metabolite, which is half as potent a blocking agent as pancuronium. Less than 5% of the injected dose is recovered as 17-hydroxy metabolite and 3, 17-dihydroxy metabolite, which have been judged to be approximately 50 times less potent than pancuronium. Pancuronium exhibits strong binding to gamma globulin and moderate binding to albumin. Approximately 13% is unbound to plasma protein. In patients with cirrhosis the volume of distribution is increased by approximately 50%, the plasma clearance is decreased by approximately 22% and the elimination half-life is doubled. Similar results were noted in patients with biliary obstruction, except that plasma clearance was less than half the normal rate.

The initial total dose to achieve adequate relaxation may thus be high in patients with hepatic and/or biliary tract dysfunction, while the duration of action is greater than usual.

The elimination half-life is doubled and the plasma clearance is reduced by approximately 60% in patients with renal failure. The volume of distribution is variable and in some cases elevated.

The rate of recovery from neuromuscular blockade, as determined by peripheral nerve stimulation, is variable and sometimes very much slower than normal.

INDICATIONS AND CLINICAL USES

PANCURONIUM BROMIDE INJECTION is indicated as an adjunct to general anesthesia to facilitate tracheal intubation and to induce skeletal muscle relaxation during surgery. It may also be employed to facilitate the management of patients requiring mechanical ventilation.

CONTRAINDICATIONS

PANCURONIUM BROMIDE INJECTION is contraindicated in patients with known hypersensitivity to the drug or to the bromide ion and in pregnant and lactating women, since animal studies have not been performed (See PRECAUTIONS: Use in Pregnancy).

In newborn infants (children less than 1 month of age), benzyl alcohol has been associated with an increased incidence of neurological and other complications which are, sometimes, fatal. As Pancuronium contains benzyl alcohol, it should not be used in newborn infants.

WARNINGS

PANCURONIUM BROMIDE INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSES BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Pancuronium may have profound effects (Known clinical pharmacology of established nondepolarizing muscle relaxants, e.g. d-tubocurarine, dictates this warning).

In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PANCURONIUM BROMIDE INJECTION contains benzyl alcohol, a preservative that has been reported to be associated with a fatal "gasping syndrome" in premature infants.

PRECAUTIONS

USE OF A PERIPHERAL NERVE STIMULATOR WILL USUALLY BE OF VALUE FOR MONITORING OF NEUROMUSCULAR BLOCKING EFFECT, AVOIDING OVERDOSAGE AND ASSISTING IN EVALUATION OF RECOVERY.

General

Although pancuronium has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations.

Renal Failure

A major portion of pancuronium, as well as an active metabolite are recovered in urine.

The elimination half-life is doubled and the plasma clearance is reduced in patients with renal failure; at the same time, the rate of recovery of neuromuscular blockade is variable and sometimes very much slower than normal (see Pharmacokinetics).

This information should be taken into consideration if Pancuronium Bromide Injection is selected, for other reasons, to be used in a patient with renal failure.

Altered Circulation Time

The onset of action of neuromuscular blocking agents may be delayed in patients who have increased volume of distribution as a result of old age, edematous states, or cardiovascular disease. In these patients, more time should be permitted for the drug to achieve its maximum effect. Increased dosage should be avoided, owing to the possibility of a markedly prolonged duration of action.

Hepatic and/or Biliary Tract Disease

The doubled elimination half-life and reduced plasma clearance determined in patients with hepatic and/or biliary tract disease, as well as limited data showing that recovery time is prolonged an average of 65% in patients with biliary tract obstruction, suggests that prolongation of neuromuscular blockade may occur. At the same time, these conditions are characterized by an approximately 50% increase in volume of distribution of pancuronium; suggesting that the total initial dose to achieve adequate relaxation may in some cases be high. The possibility of slower onset, higher total dosage and prolongation of neuromuscular blockade must be taken into consideration when pancuronium is used in these patients (See also Pharmacokinetics).

Severe Obesity or Neuromuscular Disease

Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as pancuronium.

Pancuronium has no known effect on consciousness, the pain threshold or cerebration. Administration should be accompanied by adequate anesthesia.

Sensitivity / Resistance

Anaphylaxis

Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. These reactions have in some cases been life-threatening and fatal. Due to the potential severity of these reactions, the necessary precautions, such as immediate availability of appropriate emergency treatment, should be taken.

Precautions should also be taken in those individuals who have had previous anaphylactic reactions to other neuromuscular blocking agents since cross-reactivity between neuromuscular blocking agents has been reported in this class of drugs.

Drug Interactions

Prior administration of succinylcholine may enhance the neuromuscular blocking effect of pancuronium and increase its duration of action. If succinylcholine is used before pancuronium then the administration of pancuronium should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade.

If a small dose of pancuronium is given at least 3 minutes prior to the administration of succinylcholine, in order to reduce the incidence and intensity of succinylcholine-induced fasiculations, this dose may induce a degree of neuromuscular block sufficient to cause respiratory depression in some patients.

Other nondepolarizing neuromuscular blocking agents (vecuronium, atracurium, d-tubocurarine, metocurine, and gallamine) behave in a clinically similar fashion to pancuronium. The combinations of pancuronium-metocurine and pancuronium-d-tubocurarine are significantly more potent than the additive effects of each of the individual drugs given alone. However, the duration of blockade of these combinations is not prolonged.

There are insufficient data to support concomitant use of pancuronium and the other three above mentioned muscle relaxants in the same patient.

Inhalational Anesthetics

Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with pancuronium will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents, the intubating dose of pancuronium may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium. The relatively long duration of action of pancuronium should be taken into consideration when the drug is selected for intubation in these circumstances.

Clinical experience and animal experiments suggest that pancuronium should be given with caution to patients receiving chronic tricyclic antidepressant therapy who are anesthetized with halothane because severe ventricular arrhythmias may result from this combination. The severity of the arrhythmias appear in part related to the dose of pancuronium.

Antibiotics

Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify, or produce neuromuscular block on their own.

The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B, colistin, and sodium colistimethate.

If these or other newly introduced antibiotics are used preoperatively or in conjunction with pancuronium during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other

Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for pancuronium.

Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade.

Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Use in Pregnancy

The safe use of PANCURONIUM BROMIDE INJECTION with respect to possible adverse effects upon fetal development has not been established.

The drug should therefore not be used in women of childbearing potential and particularly during early pregnancy, unless in the judgment of the physician, the potential benefits outweigh the possible risks.

Pancuronium may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade.

Dosage should usually be reduced, as indicated, in such cases. It is also recommended that the interval between use of pancuronium and delivery be reasonably short to avoid clinically significant placental transfer.

Use in Children

Neonates are particularly sensitive to the action of most nondepolarizing neuromuscular agents such as pancuronium, during the first month of life and respond with prolonged neuromuscular blockade to usual doses of the drugs. Therefore, they should be carefully monitored (See DOSAGE AND ADMINISTRATION).

The prolonged use of PANCURONIUM BROMIDE INJECTION for the management of neonates undergoing mechanical ventilation has been associated, in rare cases, with severe skeletal

muscle weakness that may first be noted during attempts to wean such patients from the ventilator; such patients usually receive other drugs such as antibiotics which may enhance neuromuscular blockade.

Microscopic changes consistent with disuse atrophy have been noted at autopsy. Although a cause-and-effect relationship has not been established, the benefits-to-risk ratio must be considered when there is a need for neuromuscular blockade to facilitate long-term mechanical ventilation of neonates.

Rare cases of unexplained, clinically significant methemoglobinemia have been reported in premature neonates undergoing emergency anesthesia and surgery which included combined use of pancuronium, fentanyl and atropine. A direct cause-and-effect relationship has not been established.

Patients with Special Diseases and Conditions

Malignant hyperthermia is a rare but often fatal reaction associated with the use of neuromuscular blocking agents and/or potent inhalation anesthetics. Heredity appears to be a factor in this reaction, because several families have been shown to have high incidence of hyperthermia. Pancuronium Bromide Injection should therefore either not be used in such patients or if necessary, patients should be carefully monitored.

As with all other neuromuscular blocking agents, PANCURONIUM BROMIDE INJECTION should be used with caution in patients with renal, hepatic, or pulmonary impairment. Pancuronium Bromide Injection should be used with extreme caution, if at all, in patients with myasthenia gravis.

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

ADVERSE EFFECTS

Neuromuscular: The most frequent adverse reaction to nondepolarizing neuromuscular blocking agents as a class consists of an extension of their pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. Appropriate treatment should be instituted. (See PRECAUTIONS: USE IN CHILDREN).

Inadequate reversal of the neuromuscular blockade is possible with pancuronium, as with all curariform drugs. These adverse experiences are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: Cardiovascular changes and bronchospasm, should they occur, are difficult to assess as these can be influenced by other factors such as premedication, induction agent, intubation, presence of an endotracheal tube, inhalation agent, pre-existing disease and dosage. (SEE ACTION AND CLINICAL PHARMACOLOGY: CIRCULATORY EFFECT).

It has been estimated that approximately 10 to 12% of patients may exhibit mild to moderate increases in blood pressure and/or pulse rate.

Gastrointestinal: Excessive salivation is sometimes noted during very light anesthesia, particularly in children or if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pancuronium Bromide Injection.

Miscellaneous: Rare hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia and other reactions possibly mediated by histamine release have been reported.

Prolonged apnea may occur when a depolarizing agent such as succinylcholine is used for intubation prior to administration of pancuronium (see DRUG INTERACTIONS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The possibility of iatrogenic overdosage can be minimized by carefully monitoring the muscle twitch response to peripheral nerve stimulation.

Excessive doses of pancuronium can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with pancuronium as with other neuromuscular blockers.

This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and to help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia, such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured.

Pyridostigmine, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate, will usually antagonize the skeletal muscle relaxant action of pancuronium. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A

peripheral nerve stimulator may also be used to monitor restoration of twitch response.

Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own.

Under such circumstances, the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration.

For management of a suspected drug overdose, contact your Regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

PANCURONIUM BROMIDE INJECTION is for intravenous use only. Pancuronium should be used only where full facilities, drugs and equipment for anesthesia and/or resuscitation are available, and under the direct supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. (See WARNINGS).

DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. The dosage information which follows have been derived from dose-response studies based on body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of pancuronium by volatile anesthetics and by prior administration of succinylcholine (see PRECAUTIONS: DRUG INTERACTIONS).

To obtain maximum clinical benefits of pancuronium and to minimize the possibility of overdosage, the monitoring of muscle twitch response by a peripheral nerve stimulator is advised.

Adults

An initial intravenous dose of 0.06 to 0.1 mg/kg usually provides rapid and generally satisfactory skeletal muscle relaxation for endotracheal intubation, usually within 2 to 2 ½ minutes.

The duration of action of the initial dose may average about 60 to 90 minutes but this can vary widely (30 to 150 minutes, or even longer) depending on dose and because of the variables mentioned above. Depending on the anticipated length of the surgical procedures, incremental doses may range from 0.5 to 1 mg. It should be emphasized that repeated doses are cumulative and produce a longer duration of action so that the higher dose need rarely be exceeded.

The usual initial dose of pancuronium bromide as an adjunct to balanced anesthesia is 0.04 to 0.1 mg/kg. Later incremental doses starting at 0.01 mg/kg may be used.

Cesarean Section

The dosage to provide relaxation for intubation and operation is the same as for general surgical procedures. The dosage to provide relaxation, following usage of succinylcholine for intubation is the same as for general surgical procedures. Dosage should be reduced in those women receiving magnesium sulfate for toxemia of pregnancy, since magnesium salts enhance neuromuscular blockade (See PRECAUTIONS: DRUG INTERACTIONS).

Children

Dose response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. In general, an initial intravenous dose of 0.06 to 0.1 mg/kg usually provides satisfactory relaxation and ease of intubation in most surgical procedures.

If succinylcholine is used for intubation, then the initial relaxant dose should be decreased by about one-third. Incremental doses should be 0.01 mg/kg.

As neonates are especially sensitive to nondepolarizing neuromuscular blocking agents during the first month of life, it is recommended that a test dose of 0.02 mg/kg be given to measure responsiveness.

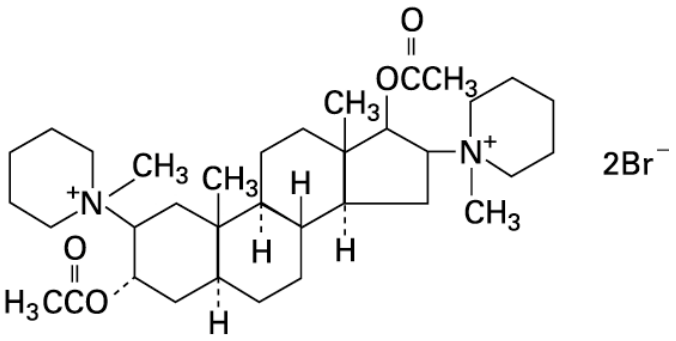
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Pancuronium bromide BP

Chemical Name: 1,1'-(3α,17β-Dihydroxy-5α-androstan-2β,-16β-ylene)bis [1-methylpiperidinium]dibromide diacetate

Structural Formula:



Molecular Formula: $C_{35}H_{60}Br_2N_2O_4$

Molecular Weight: 732.68

Description:

Pancuronium bromide occurs as a fine white, odorless, hygroscopic powder that is freely soluble in water, very soluble in alcohol and chloroform. It is sensitive to heat and melts at 215 °C.

Composition:

PANCURONIUM BROMIDE INJECTION is a sterile, isotonic, nonpyrogenic solution for injection. Each mL contains pancuronium bromide 1 or 2 mg; sodium acetate anhydrous 1.2 mg; benzyl alcohol 10 mg (as preservative). Sodium chloride added to adjust tonicity. May contain acetic acid and/or sodium hydroxide for pH adjustment; pH 4.0 (3.8 to 4.2).

Compatibility:

PANCURONIUM BROMIDE INJECTION is compatible in solution with:

0.9% Sodium Chloride Injection
5% Dextrose Injection
5% Dextrose and Sodium Chloride Injection
Lactated Ringer's Injection

When mixed with the above solutions in glass or plastic containers, pancuronium will remain stable in solution for 24 hours with no alteration in potency or pH; no decomposition is observed and there is no absorption to either the glass or plastic container.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permits.

Stability and Storage Recommendations:

PANCURONIUM BROMIDE INJECTION should be stored under refrigeration (2° - 8°C).

AVAILABILITY OF DOSAGE FORMS

PANCURONIUM BROMIDE INJECTION is available in single dose ampoules and multiple dose vials as follows:

-2 mg/mL in 2 mL (4 mg/2 mL) Ampoules, List L257
-2 mg/mL in 4 mL (8 mg/4 mL) Ampoules, List L257

-1 mg/mL in 5 mL (5 mg/5 mL) Fliptop Vials, List L258
-1 mg/mL in 10 mL (10 mg/10 mL) Fliptop Vials, List L258

PHARMACOLOGY

Animal Pharmacology

Pancuronium bromide is a highly specific and potent neuromuscular blocking agent of medium duration. The neuromuscular blocking action has been demonstrated in mice, rats, rabbits, cats and dogs.

Intravenous administration of pancuronium in doses ranging from 0.02 to 0.05 mg/kg, produced blockade of the twitches of the gastrocnemius muscle of the cat elicited by sciatic nerve stimulation.

During this blockade, direct muscle stimulation led to normal contractions. In experiments evoking nerve and muscle action potential simultaneously, the same doses of pancuronium abolished the muscle action potentials whereas the nerve action potentials were unaffected. Results clearly indicate the site of action of pancuronium to be at the neuromuscular junction.

The following studies conducted in anesthetized cats have given evidence for the nondepolarizing mode of action of pancuronium bromide.

- The intravenous injection of pancuronium bromide blocked the tibialis muscle contractions evoked by the arterial injection of acetylcholine.
- Edrophonium and neostigmine given intravenously rapidly and completely reverse the neuromuscular block produced.
- Succinylcholine, potassium ions and adrenaline injected intravenously antagonized the block.
- A small dose of tubocurarine augmented the pancuronium bromide induced block of the sciatic gastrocnemius preparation.
- During partial neuromuscular block, tetanus was poorly sustained and post-tetanic facilitation was observed.
- Hypothermia reduced the intensity of the block.

These findings were confirmed and extended in experiments with other species. No contractual response was seen in response to pancuronium bromide in avian (chicken) or frog muscle, whereas the drug antagonized the muscle contractions in the isolated frog rectus abdominis muscle preparation.

All of these results are characteristic of blocking drugs of the nondepolarizing type.

The species sensitivity to pancuronium shows that, on a mg/kg experimental basis, man is the least sensitive species, as can be seen from Table 1.

Table 1 **The species sensitivity to Pancuronium**		
Species	Test	Effective Blocking Dose (mg/kg) (± S.D.)
Man	Ulnar-hypothenar	0.05
Mouse	Grip strength	0.03 (0.024 to 0.046)
Dog	Sciatic-gastrocnemius	0.015 (0.007 to 0.024)
Cat	Sciatic-gastrocnemius	0.013
Rabbit	Sciatic-gastrocnemius	0.008 (0.007 to 0.009)

In most species the duration of action is similar to that of tubocurarine.

Ganglionic-blocking activity assessed by the cat cervical sympathetic nerve nictitating membrane preparation was one-eighth that of hexamethonium. Weak activity was also seen in the isolated nicotine-stimulated guinea pig ileum preparation. In none of the experiments on anesthetized animals did pancuronium produce a drop in blood pressure, confirming that its ganglionic blocking activity is weak.

Histamine release does not occur following injection of pancuronium bromide. In the anesthetized guinea pig no bronchoconstriction was seen even after doses of 10 mg/kg and in the ganglion-blocked anesthetized cat no delayed pressure response was observed. Similarly, no histamine release could be detected biochemically in rabbit following large doses of pancuronium.

Atropine-like Activity

Pancuronium bromide is almost devoid of atropine like activity when assessed on the isolated guinea pig ileum. The drug has the order 10^{-8} the activity of atropine.

Metabolic studies in dogs using radioactive pancuronium bromide showed that 33 to 62% of the administered dose is excreted in the urine in the first 3 hours. After 24 hours, radioactivity is demonstrated in the liver and certain other organs and is slowly released thereafter. Pancuronium bromide is metabolized in the liver by the hydrolysis of either or both of its ester radicals to inactive hydroxy derivatives (3 mono-, 17 mono-and 3,17 dideacetylated derivatives). Large amounts of the metabolites are then excreted in the feces.

TOXICOLOGY

Acute Toxicity

The acute toxicity of pancuronium bromide, administered by a variety of routes, was studied in mice, rats and rabbits. The LD_{50} values obtained in these species are as follows in Table 2:

Table 2
Acute LD50 Values of Pancuronium

Species	Route	LD_{50} (mg/kg)
Mice	i.v.	0.047
	S.C.	0.167
	I.P.	0.152
	P.O.	21.9
Rats	i.v.	0.153
	S.C.	
	I.P.	
	P.O.	
Rabbits	i.v.	0.016
	S.C.	
	I.P.	
	P.O.	

The acute toxicity of pancuronium bromide is related to its neuromuscular blocking activity, since in all cases death was caused by respiratory failure. The results in mice indicate that toxicity is greatest following intravenous injection.

In cats under artificial respiration, very large doses of pancuronium bromide could be administered without signs of toxicity. In this species doses of up to 25,000 times the effective neuromuscular blocking dose could be given without mortality, provided adequate ventilation was maintained.

Subacute Toxicity

Subacute toxicity studies were carried out in dogs and cats given 10 consecutive infusions of either 3.75 mg/kg or 15.0 mg/kg (over a period of 12 to 14 days in dogs or 22 to 26 days in cats), which approximate 50 to 200 times the average human dose of 0.07 mg/kg.

In dogs, no mortality was observed at either dosage level, and although cats took longer to recover due to their greater sensitivity to pancuronium, in both species no adverse clinical or histopathological effects were reported. Some cardiac effects (mainly tachycardia) which could be attributed to the drug were observed in both species.

Reproduction and Teratology

In groups of rats given daily intraperitoneal doses of 0.16 mg/kg pancuronium, either from the 7th to 14th day or the 1st to the 20th days of the gestation period, no adverse effects were noted on the fetuses examined at birth or after removal by Cesarean section on the 21st day. The drug had no effect on the number of fetuses, their viability or weight, number of resorptions, influence on the frequency or the number of gross malformations, malformations of internal organs, and skeletal malformations.

Similar results were obtained in a group of rabbits given daily intravenous doses of 0.02 mg/kg from the 8th to the 16th days of the gestation period.

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PART III: CONSUMER INFORMATION

Pancuronium Bromide Injection

This leaflet is part III of a three-part "Product Monograph". This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Pancuronium Bromide Injection. Contact your doctor or nurse if you have any questions about this drug.

ABOUT THIS MEDICATION

What the medication is used for:

Pancuronium Bromide Injection is used as part of the general anesthetic. It relaxes muscles during an operation, including a caesarean section. It can also be used to ease mechanical ventilation which helps you breathe.

What it does:

Pancuronium Bromide Injection blocks the nerve impulses to move your muscles. Because the muscles needed for breathing also become relaxed, you will need help breathing (mechanical ventilation) during and after your operation until you can breathe on your own. At the end of surgery, the effects of Pancuronium Bromide Injection will wear off so you can start breathing on your own.

When it should not be used:

- if you have had an allergic reaction to pancuronium, to bromide, or any of the other ingredients in Pancuronium Bromide Injection.
- if you are pregnant or breastfeeding.
- in newborns less than 1 month of age. Pancuronium Bromide Injection contains benzyl alcohol, a preservative that has been associated with fatal complications including "gasping syndrome" in premature infants.

What the medicinal ingredient is:

Pancuronium bromide.

What the nonmedicinal ingredients are:

Benzyl alcohol, Sodium acetate anhydrous, and sodium chloride. May also contain acetic acid and/or sodium hydroxide.

What dosage forms it comes in:

Single dose ampoules: 2 mg/mL (2 mL and 4 mL)
Multiple dose vials: 1 mg/mL (5 mL and 10 mL).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

As for all drugs used during an operation, this drug should be administered only in a facility prepared to give resuscitation and life support by adequately trained health care professionals familiar with its actions, characteristics, and hazards.

Your medical history can influence the way that Pancuronium Bromide Injection is given to you.

BEFORE you receive Pancuronium Bromide Injection talk to your doctor if you have:

- myasthenia gravis or myasthenic (Eaton-Lambert) syndrome or other neuromuscular diseases
- cancer, particularly lung cancer
- decreased kidney function or kidney disease
- heart disease or heart valve disease
- severe obesity
- pulmonary hypertension or lung disease
- oedema (fluid retention for example at the ankles)
- recent, severe vomiting, diarrhea, and "water pill" use
- liver or gallbladder disease or decreased liver function
- diseases affecting nerves or muscles
- an allergy to muscle relaxants.
- a history or family history of malignant hyperthermia (sudden fever with stiffness and pain in your muscles, rapid breathing and pulse)

Tell your doctor if you have any other medical conditions, as they may influence how Pancuronium Bromide Injection works.

Driving and Using Machines

Your doctor will inform you when it is safe to drive and operate potentially dangerous machinery after you have been administered Pancuronium Bromide Injection.

INTERACTIONS WITH THIS MEDICATION

It is very important to tell your doctor about any medications you may be taking, including medicines obtained without a prescription. This will help your doctor to decide the correct dose of Pancuronium Bromide Injection for you.

Be sure to tell about any antibiotics and medications for diseases which lead to electrolyte imbalance such as adrenal cortical insufficiency or medication to counter electrolyte imbalance such as magnesium salts.

PROPER USE OF THIS MEDICATION

Usual dose:

The dose given is decided by the doctor based on the clinical need

and your physical condition.

Only an adequately trained health care professional may give Pancuronium Bromide Injection.

Overdose:

As medical personnel will be monitoring your condition during the procedure it is unlikely that you will be given too much Pancuronium Bromide Injection. However, if this happens artificial respiration will be continued until you are able to breathe again on your own. It is possible to counteract the effects of (too much) Pancuronium Bromide Injection and speed-up your recovery by giving you a drug that reverses the effects of Pancuronium Bromide Injection.

Pancuronium Bromide Injection will be given under the supervision of a qualified physician who will manage your condition in the event of an overdose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Pancuronium Bromide Injection can have side effects. **Your anaesthetist or intensive care doctor will care for you if any of the following side effects or any other undesirable events occur.**

AFTER SURGERY

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

For the following serious side effects, you must seek immediate emergency medical treatment.

- Allergic reactions (rash, swelling of the face, throat, lips, difficulty breathing).
- Feeling cold and/or clammy
- Difficulty breathing/choking/wheezing
- Muscle weakness or paralysis
- Rapid or slow heart beat
- Sudden fever with stiffness, pain and weakness in your muscles
- Seizure/seizure-like activity

For the following serious side effects, call your doctor or pharmacist.

- Dizziness especially upon standing up quickly
- High or low blood pressure if measured
- Severe itching
- Increase in blood pressure
- Jaundice/yellowing of the skin/eyeballs
- Problems with your vision
- Excessive salivation (drooling)
- Skin rash

This is not a complete list of side effects. For any unexpected effects after receiving Pancuronium Bromide Injection, contact your doctor or nurse.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Hospira Healthcare Corporation, at: 1-866-488-6088, Option 4.

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