Pancuronium

Generic Name: Pancuronium bromide
Dosage Form: Injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

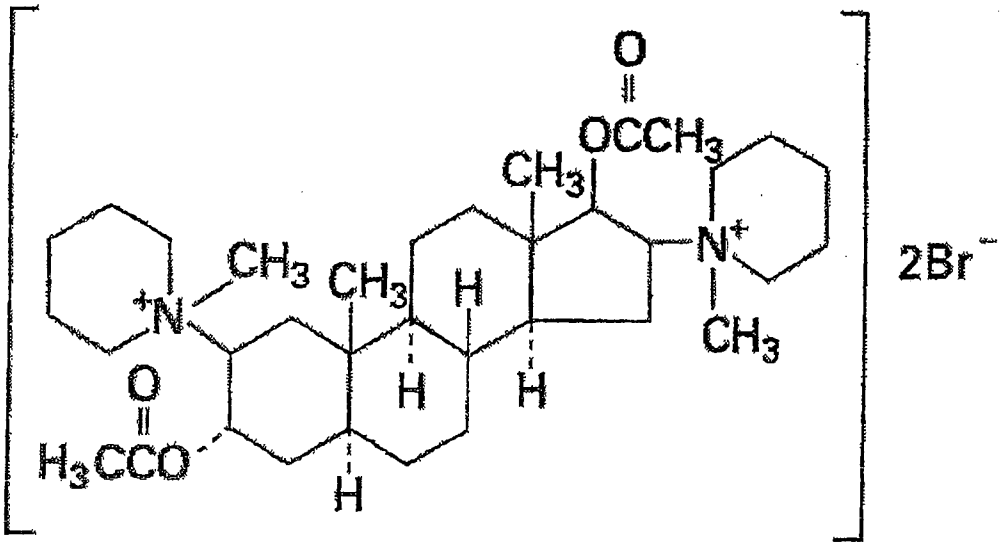
1 mg/mL Fliptop Vial

R_x only

Pancuronium Description

Pancuronium Bromide is a nondepolarizing neuromuscular blocking agent chemically designated as the aminosteroid 2β, 16β - dipiperidino-5α-androstane-3α, 17-β diol diacetate dimethobromide, $C_{35}H_{60}Br_2N_2O_4$. It is a fine white odorless powder which is soluble in water, alcohol and chloroform.

It has the following structural formula:



Pancuronium Bromide Injection is available in sterile, isotonic, nonpyrogenic solution for injection. Each mL contains Pancuronium bromide 1 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 is 4.0 (3.8 to 4.2).

Pancuronium - Clinical Pharmacology

Pancuronium bromide 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 bromide is approximately 1/3 less potent than vecuronium and approximately 5 times as potent as d-tubocurarine; the duration of neuromuscular blockage produced by Pancuronium bromide is longer than that of vecuronium at initially equipotent doses.

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 use of a peripheral nerve stimulator is of benefit in assessing the degree of neuromuscular blockade.

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.

Data on histamine assays and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are rare. (See ADVERSE REACTIONS).

Pharmacokinetics

The elimination half-life of Pancuronium has been reported to range between 89-161 minutes. The volume of distribution ranges from 241-280 mL/kg; and plasma clearance is approximately 1.1–1.9 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 of neuromuscular blockade, as determined by peripheral nerve stimulation is variable and sometimes very much slower than normal.

Indications and Usage for Pancuronium

Pancuronium bromide is indicated as an adjunct to general anesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

Contraindications

Pancuronium Bromide Injection is contraindicated in patients known to be hypersensitive to the drug.

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 bromide may have profound effects. 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.

Benzyl alcohol has been reported to be associated with a fatal "gasping syndrome" in premature infants.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to those received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including Pancuronium) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of Pancuronium bromide for

premature and term infants includes amounts of benzyl alcohol well below that associated with toxicity; however, the amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources.

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 Bromide Injection 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 is selected, for other reasons, to be used in a patient with renal failure.

Altered Circulation Time

Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore, dosage should not be increased.

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).

Long-term Use in I.C.U.

In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance, and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered.

Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

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 bromide.

CNS

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

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 bromide, the administration of Pancuronium bromide should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade.

...ging be given first in this group to measure responsiveness.

The prolonged use of Pancuronium bromide 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 between the combined use of these drugs and the reported cases of methemoglobinemia has not been established.

Adverse Reactions

Neuromuscular

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. (See PRECAUTIONS: Pediatric Use).

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

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit.

Cardiovascular

See discussion of circulatory effects in CLINICAL PHARMACOLOGY.

Gastrointestinal

Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin

An occasional transient rash is noted accompanying the use of Pancuronium bromide.

Other

Although histamine release is not a characteristic action of Pancuronium bromide, rare hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia and other reactions possibly mediated by histamine release have been reported.

Overdosage

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

Excessive doses of Pancuronium bromide can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed may occur with Pancuronium bromide 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 help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Pyridostigmine bromide, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate, will usually antagonize the skeletal muscle relaxant action of Pancuronium bromide. 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. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

Pancuronium Dosage and Administration

Pancuronium bromide is given at least 3 minutes prior to the administration of succinylcholine, in order to reduce the incidence and intensity of succinylcholine-induced fasciculations, 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 bromide. The combination of Pancuronium bromide-metocurine and Pancuronium bromide-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 bromide will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents, the intubating dose of Pancuronium bromide 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 bromide, 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 bromide.

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.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C

Animal reproduction studies have not been performed. It is not known whether Pancuronium bromide can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pancuronium bromide should be given to a pregnant woman only if the administering clinician decides that the benefits outweigh the risks.

Pancuronium bromide may be used in operative obstetrics (Caesarean 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.

Pediatric Use

Dose response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Neonates are especially sensitive to nondepolarizing neuromuscular blocking agents, such as Pancuronium bromide, during the first month of life. It is recommended that a test dose of

Pancuronium Bromide Injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only. Since potent inhalational anesthetics or prior use of succinylcholine may enhance the intensity and duration of Pancuronium bromide (see PRECAUTIONS: Drug Interactions), the lower end of the recommended initial dosage range may suffice when Pancuronium bromide is first used after intubation with succinylcholine and/or after maintenance doses of volatile liquid inhalational anesthetics are started. To obtain maximum clinical benefits of Pancuronium Bromide Injection and to minimize the possibility of overdosage, the monitoring of muscle twitch response to a peripheral nerve stimulator is advised.

In adults under balanced anesthesia the initial intravenous dosage range is 0.04 to 0.1 mg/kg. Later incremental doses starting at 0.01 mg/kg may be used. These increments slightly increase the magnitude of the blockade and significantly increase the duration of blockade because a significant number of myoneural junctions are still blocked when there is clinical need for more drug.

If Pancuronium Bromide Injection is used to provide skeletal muscle relaxation for endotracheal intubation, a bolus dose of 0.06 to 0.1 mg/kg is recommended. Conditions satisfactory for intubation are usually present within 2 to 3 minutes (see PRECAUTIONS).

Dosage in Children

Dose response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Neonates are especially sensitive to nondepolarizing neuromuscular blocking agents, such as Pancuronium Bromide Injection, during the first month of life. It is recommended that a test dose of 0.02 mg/kg be given first in this group to measure responsiveness.

Caesarean 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 (see PRECAUTIONS: Drug Interactions), is the same as for general surgical procedures.

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

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

When mixed with the above solutions in glass or plastic containers, Pancuronium Bromide Injection will remain stable in solution for 48 hours with no alteration in potency or pH; no decomposition is observed and there is no absorption to either the glass or plastic container.

How Is Pancuronium Supplied

Pancuronium Bromide Injection is supplied as follows:

List No.		Container
4646	Multiple-dose	10 mL Fliptop Vial—1 mg/mL
		cartons of 25

STORAGE

Store in refrigerator 2° to 8°C (36° to 46°F).

The 10mL vial will maintain full clinical potency for up to six months at room temperature.

November, 2004

HOSPIRA, INC., LAKE FOREST, IL 60045 USA

Pancuronium Bromide (Pancuronium Bromide)

Product Code	0409-4646	**Dosage Form**	INJECTION, SOLUTION
Route Of Administration	INTRAVENOUS	**DEA Schedule**	

INGREDIENTS

Name (Active Moiety)	Type	Strength
Pancuronium Bromide (Pancuronium)	Active	1 MILLIGRAM In 1 MILLILITER
Sodium Acetate Anhydrous	Inactive	1.2 MILLIGRAM In 1 MILLILITER
Benzyl Alcohol	Inactive	10 MILLIGRAM In 1 MILLILITER
Sodium Chloride	Inactive	
Acetic Acid	Inactive	
Sodium Hydroxide	Inactive	

IMPRINT INFORMATION

Characteristic	Appearance	Characteristic	Appearance
Color		**Score**	
Shape		**Symbol**	
Imprint Code		**Coating**	
Size			

PACKAGING

#	NDC	Package Description	Multilevel Packaging
1	0409-4646-01	4 BOX In 1 CASE	contains a BOX (0409-4646-01)
1	0409-	25 VIAL In 1 BOX	This package is contained within the CASE (0409-4646-01) and contains a

	4646-01		VIAL, MULTI-DOSE (0409-4646-01)
1	0409-4646-01	10 MILLILITER In 1 VIAL, MULTI-DOSE	This package is contained within a BOX (0409-4646-01) and a CASE (0409-4646-01)

Revised: 10/2006

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CENTRATIONS FOR VARIOUS CONCENTRATIONS

Concentration Desired		Amounts to Use	
		Pentothal	Diluent
ercent	mg/mL	g	mL
0.2	2	1	500
0.4	4	1	250
		2	500
2.0	20	5	250
		10	500
2.5	25	1	40
		5	200
5	50	1	20
		5	100

stituted solutions of Pentothal (Thiopental Sodium ium, USP) should be inspected visually for particu- ter and discoloration, whenever solution and con- ner permit.

PPLIED

l is available in a variety of sizes and containers t the end of this insert.

s in
ial® Kits
D-MIX SYRINGES AND VIALS

aring solutions of Thiopental Sodium
ium, USP)

TION

aring diluents in various container, syringe and vial provided in Pentothal Kits, Pentothal Ready-to-Mix and Vials for preparing solutions of Pentothal tal Sodium for Injection, USP) for clinical use:

Water for Injection, USP is a sterile, nonpyrogenic ion of water for injection which contains no ital, antimicrobial agents or added buffers. The pH to 7.6)

Water for Injection, USP is a pharmaceutic aid for intravenous administration only after addition of

is chemically designated H_2O.

Sodium Chloride Injection, USP is a sterile, pyrogen, isotonic solution of sodium chloride and water ion. Each mL contains sodium chloride 9 mg (.9% ight per vol). It contains no bacteriostat, antimicrobial r added buffers except for pH adjustment. May ave hydrochloric acid and/or sodium hydroxide for pH ust. pH is 4.7 (4.5 to 7.0).

odium Chloride Injection, USP is an isotonic vehicle renous administration of another solute.

n chloride is chemically designated NaCl, a white e compound freely soluble in water.

ne-rigid vial contained in List Nos. 3529, 6418, 6419, 1 6435 is fabricated from a specially formulated n. It is a copolymer of ethylene and propylene. The ne plastic has been confirmed by tests in animals g to USP biological standards for plastic rs. The container requires no vapor barrier to the proper labeled volume.

PHARMACOLOGY

ater for Injection, USP serves only as a pharmaceutic ucting or dissolving drugs prior to administration.

s an essential constituent of all body tissues and s for approximately 70% of total body weight. normal adult daily requirement ranges from two to rs (1.0 to 1.5 liters each for insensible water loss by ion and urine excretion).

Water balance is maintained by various regulatory mechanisms. Water distribution depends primarily on the concentration of dissociated electrolytes in the body compartments and sodium (Na^+) plays a major role in maintaining a physiologic equilibrium between fluid intake and output.

0.9% Sodium Chloride Injection, USP serves only as an isotonic vehicle for drugs prior to administration.

Sodium chloride in water is an electrolyte solution of sodium (Na^+) and chloride (Cl^-) ions. These ions are normal constituents of the body fluids (principally extracellular) and are essential for maintaining electrolyte balance.

The distribution and excretion of sodium (Na^+) and chloride (Cl^-) are largely under the control of the kidney which maintains a balance between intake and output of these ions.

The small volumes of fluid and amounts of sodium chloride provided by 0.9% Sodium Chloride Injection in Ready-to-Mix Syringes are unlikely to produce a significant effect on fluid or electrolyte balance.

INDICATIONS AND USAGE

These products are indicated only for preparing Pentothal (Thiopental Sodium for Injection, USP) solutions for clinical use.

CONTRAINDICATIONS

Do not use unless the diluent is clear and the bottle or vial seal or syringe package is undamaged.

Diluents in Pentothal Kits, Ready-to-Mix Syringes or Vials should not be used for fluid or sodium chloride replacement.

WARNINGS

Intravenous administration of Sterile Water for Injection, USP without a solute may result in hemolysis.

Use aseptic technique for preparing Pentothal solutions when using Pentothal Kits, Syringes or Vials and during withdrawal from reconstituted single or multiple-use containers.

Administer only clear reconstituted solutions.

Use within 24 hours after reconstitution. Discard unused portions.

PRECAUTIONS

Do not use unless solution is clear and container is undamaged.

Inspect reconstituted (mixed) solutions of Pentothal (Thiopental Sodium for Injection, USP) for clarity and freedom from precipitation or discoloration prior to administration. Use reconstituted solution only if it is clear, free from precipitate and not discolored.

Use Transfer Label in each Pentothal Kit and affix to container of reconstituted solution to show concentration and time of preparation.

Pregnancy Category C. Animal reproduction studies have not been conducted with sterile water for injection or sodium chloride injection. It is also not known whether sterile water or sodium chloride injection containing additives can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sterile water for injection or sodium chloride injection with additives should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Reactions which may occur because of the diluents, techniques of preparation or mixing, or administration of reconstituted solutions of Pentothal include febrile response or infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection and extravasation.

If an adverse reaction does occur, discontinue the injection, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of unused solution (or the used container or syringe) for examination if deemed necessary.

DRUG ABUSE AND DEPENDENCE

None known.

OVERDOSAGE

Used as diluents for preparing solutions of Pentothal (Thiopental Sodium for Injection, USP) the small volumes of administered fluid from Sterile Water for Injection in bottles and vials and amounts of sodium chloride (from 0.9% Sodium Chloride Injection in Ready-to-Mix Syringes) are unlikely to pose a threat of fluid or sodium chloride overload.

DOSAGE AND ADMINISTRATION

Pentothal solutions should be administered only by intravenous injection and by individuals experienced in the conduct of intravenous anesthesia.

The volume and choice of diluent for preparing Pentothal (Thiopental Sodium for Injection, USP) solutions for clinical use depends on the concentration and vehicle desired. Pentothal Kits provide only Sterile Water for Injection as the diluent for individual or multi-patient use; Pentothal Ready-to-Mix Syringes provide only 0.9% Sodium Chloride Injection, USP as the diluent for individual patient use; vials provide only Sterile Water for Injection, USP as the diluent for individual patient use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See PRECAUTIONS.

HOW SUPPLIED

The diluent in Pentothal Kits is supplied in various-size containers with various dosage sizes of Pentothal (Thiopental Sodium for Injection, USP). Kits include all items needed for aseptic transfer of Pentothal powder from a squeeze bottle into the diluent container.

The diluent in Pentothal Ready-to-Mix Syringes is supplied in a separate container to permit mixing with the Pentothal in a powder vial to permit immediate intravenous injection of reconstituted solution into a vein or attachment to a standard stopcock assembly.

Vials are supplied in cartons with different dosage sizes of Pentothal for preparing 2.0% or 2.5% concentrations by using a separate syringe (not supplied) for mixing.

See table for list of sizes available.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Keep reconstituted solution in a cool place.

Caution: Federal (USA) law prohibits dispensing without prescription.

Table: Pentothal® (Thiopental Sodium for Injection, USP) and Diluent in Kits, Ready-to-Mix Syringes and Ready-to-Mix UltaShield® Syringes

List No.	Pentothal	Pentothal Container	Diluent (mL)*	Diluent Container	Theoretical Reconstituted Conc.
6529 (00)	1.5 g	Squeeze Bottle	W (125)	PF Bottle	1% (20 mg/mL)
6108 (00)	5 g	Squeeze Bottle	W (250)	PF Bottle	2% (20 mg/mL)
6244 (00)	1 g	Squeeze Bottle	W (40)	PF Bottle	2.5% (25 mg/mL)
6259 (00)	2.5 g	Squeeze Bottle	W (100)	PF Bottle	2.5% (25 mg/mL)
6504 (00)	5 g	Squeeze Bottle	W (200)	Bottle	2.5% (25 mg/mL)
6435 (00)	1 g	Vial	W (50)	Plastic Vial	2% (20 mg/mL)
2834 (00)	500 mg	Vial	W (20)	Plastic Vial	2.5% (25 mg/mL)
9062 (00)	1 g	Vial	W (50)	Plastic Vial	2% (20 mg/mL)
5068 (00)	500 mg	Vial	W (20)	Plastic Vial	2.5% (25 mg/mL)
6518 (Ready-to-Mix Syringe)	400 mg	Syringe	S (20)	Syringe	2% (20 mg/mL)
6411 (Ready-to-Mix Syringe)	250 mg	Syringe	S (10)	Syringe	2.5% (25 mg/mL)
6343 (Ready-to-Mix Syringe)	500 mg	Syringe	S (20)	Syringe	2.5% (25 mg/mL)
3351 (Ready-to-Mix UltaShield Syringe)	250 mg	Syringe	S (10)	Plastic Vial	2.5% (25 mg/mL)
3352 (Ready-to-Mix UltaShield Syringe)	400 mg	Syringe	S (20)	Plastic Vial	2% (20 mg/mL)
3353 (Ready-to-Mix UltaShield Syringe)	500 mg	Syringe	S (20)	Plastic Vial	2.5% (25 mg/mL)
6411 (Ready-to-Mix Syringe)	250 mg	Syringe	W (10)	Plastic Vial	2.5% (25 mg/mL)
6411 (Ready-to-Mix Syringe)	400 mg	Syringe	W (20)	Plastic Vial	2% (20 mg/mL)
6429 (Ready-to-Mix Syringe)	500 mg	Syringe	W (20)	Plastic Vial	2.5% (25 mg/mL)

PF— Sterile Diluent for Injection, USP
W— Sterile Water for Injection, USP
S— Sterile 0.9% Sodium Chloride Injection, USP

* Diluent containers are slightly overfilled to assure compliance with USP minimum fill volume requirements.

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ABBOTT LABORATORIES, NORTH CHICAGO, ILLINOIS 60064 USA

PENTOTHAL®

THIOPENTAL SODIUM FOR INJECTION, USP

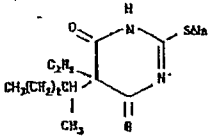
WARNING: MAY BE HABIT FORMING.

DESCRIPTION

Pentothal (Thiopental Sodium for Injection, USP) is a thiobarbiturate, the sulfur analogue of sodium pentobarbital.

The drug is prepared as a sterile powder and after reconstitution with an appropriate diluent is administered by the intravenous route.

Pentothal is chemically designated sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate and has the following structural formula:



The drug is a yellowish, hygroscopic powder, stable with anhydrous sodium carbonate as a buffer (80 mg/g t thiopental sodium).

CLINICAL PHARMACOLOGY

Pentothal (Thiopental Sodium for Injection, USP) is a ultrashort-acting depressant of the central nervous syster which induces hypnosis and anesthesia, but not analgesia. I produces hypnosis within 30 to 40 seconds of intravenous injection. Recovery after a small dose is rapid, with som drowsiness and retrograde amnesia. Repeated intravenous doses lead to prolonged anesthesia because fatty tissue act as a reservoir; they accumulate Pentothal i concentrations 5 to 12 times greater than the plasma concentration, and then release the drug slowly to cause prolonged anesthesia.

The half-life of the elimination phase after a singl intravenous dose is 6 to 8 hours.

The distribution and fate of Pentothal are with othe barbiturates is influenced chiefly by its lipid solubilit (partition coefficient), protein binding and extent o ionization. Pentothal has a partition coefficient of 580.

Approximately 80% of the drug in the blood is bound t plasma protein. Pentothal is largely degraded in the liver an to a smaller extent in other tissues, especially the kidney an brain. It has a pK_a of 7.6.

Concentration in spinal fluid is slightly less than in th plasma.

Biotransformation products of thiopental are pharma cologically inactive and mostly excreted in the urine.

INGS AND USAGE

ıl (Thiopental Sodium for Injection, USP) is indicated
ge sole anesthetic agent for brief (15 minute)
ires, (2) for induction of anesthesia prior to
rsion of other anesthetic agents, (3) to supplement
anesthesia, (4) to provide hypnosis during balanced
sia with other agents for analgesia or muscle
in, (5) for the control of convulsive states during or
) inhalation anesthesia, local anesthesia, or other
(6) in neurosurgical patients with increased
ial pressure, if adequate ventilation is provided,
or narcoanalysis and narcosynthesis in psychiatric
s.

INDICATIONS

› Contraindications:
nce of suitable veins for intravenous administration,
sensitivity (allergy) to barbiturates and (3) variegate
a (South African) or acute intermittent porphyria.

Contraindications:
e cardiovascular disease, (2) hypotension or shock,
tions in which the hypnotic effect may be prolonged
ilated — excessive premedication, Addison's
hepatic or renal dysfunction, myxedema, increased
ia, severe anemia, asthma, myasthenia gravis, and
arrhythmias.

ASS

SUCCINYLCHOLINE AND ENDOTRACHEAL INTUBATION
ENT AND OXYGEN READILY AVAILABLE.
INPATENCY OF THE AIRWAY AT ALL TIMES.
drug should be administered only by persons
in the use of intravenous anesthetics,
extravasation or intra-arterial injection.
IRED: MAY BE HABIT FORMING.

INGS

aseptic precautions at all times in preparation and
of Pentothal (Thiopental Sodium for Injection, USP)

l in conditions involving relative contraindications,
usage and administer slowly.
hould be taken in administering the drug to patients
vanced cardiac disease, increased intracranial
, ophthalmoplegic plus, asthma, myasthenia gravis
ocrine insufficiency (pituitary, thyroid, adrenal,
).

nteractions: The following drug interactions have
orted with thiopental.

g	Effect
benerid	Prolonged action of thiopental
rcaine	Hypotension
alidine	Thiopental antagonism
id analgesics	Decreased amniotic ective action
nophrine	Thiopental antagonism
ardism	Synergism

g *Mothers:* Thiopental sodium readily crosses the
barrier and small amounts may appear in the milk
mothers following administration of large doses.
ory Category C. Animal reproduction studies have
conducted with Pentothal. It is also not known
ethal can cause fetal harm when administered to
k woman or can affect reproduction capacity
should be given to a pregnant woman only if clearly

ADVERSE REACTIONS

Adverse reactions include respiratory depression, myocardial depression, cardiac arrhythmias, prolonged somnolence and recovery, sneezing, coughing, bronchospasm, laryngospasm and shivering. Anaphylactic and anaphylactoid reactions to Pentothal (Thiopental Sodium for Injection, USP) have been reported. Symptoms, e.g., urticaria, bronchospasm, vasodilation and edema should be managed by conventional means.

Rarely, immune hemolytic anemia with renal failure and radial nerve palsy have been reported.

DRUG ABUSE AND DEPENDENCE

WARNING: MAY BE HABIT FORMING.

Thiopental sodium is classified as a Schedule III controlled substance.

OVERDOSAGE

Overdosage may occur from too rapid or repeated injections. Too rapid injection may be followed by an alarming fall in blood pressure even to shock levels. Apnea, occasional laryngospasm, coughing and other respiratory difficulties with excessive or too rapid injections may occur. In the event of suspected or apparent overdosage, the drug should be discontinued, a patent airway established (intubate if necessary) or maintained, and oxygen should be administered, with assisted ventilation if necessary. The lethal dose of barbiturates varies and cannot be stated with certainty. Lethal blood levels may be as low as 1 mg/100 mL for short-acting barbiturates; less if other depressant drugs or alcohol are also present.

MANAGEMENT OF OVERDOSAGE

It is generally agreed that respiratory depression or arrest due to unusual sensitivity to thiopental sodium or overdosage is easily managed if there is no concomitant respiratory obstruction. If the airway is patent, any method of ventilating the lungs that prevents hypoxia) should be successful in maintaining other vital functions. Since depression of respiratory activity is one of the characteristic actions of the drug, it is important to observe respiration closely.

Should laryngeal spasm occur, it may be relieved by one of the usual methods, such as the use of a relaxant drug or positive pressure oxygen. Endotracheal intubation may be indicated in difficult cases.

DOSAGE AND ADMINISTRATION

Pentothal is administered by the intravenous route only. Individual response to the drug is so varied that there can be no fixed dosage. The drug should be titrated against patient requirements as governed by age, sex and body weight. Younger patients require relatively larger doses than middle-aged and elderly persons; the latter metabolize the drug more slowly. Pre-puberty requirements are the same for both sexes, but adult females require less than adult males. Dose is usually proportional to body weight and obese patients require a larger dose than relatively lean persons of the same weight.

Premedication

Premedication usually consists of atropine or scopolamine to suppress vagal reflexes and inhibit secretions. In addition, a barbiturate or an opiate is often given. Sodium pentobarbital injection (Nembutal®) is suggested because it provides a preliminary indication of how the patient will react to barbiturate anesthesia. Ideally, the peak effect of these medications should be reached shortly before the time of induction.

Test Dose

It is advisable to inject a small "test" dose of 25 to 75 mg (1 to 3 mL of a 2.5% solution) of Pentothal (Thiopental Sodium for Injection, USP) to assess tolerance or unusual sensitivity to Pentothal, and pausing to observe patient reaction for at least 60 seconds. If unexpectedly deep anesthesia develops or if respiratory depression occurs, consider these possibilities: (1) the patient may be unusually sensitive to Pentothal, (2) the solution may be more concentrated than had been assumed, or (3) the patient may have received too much premedication.

Use in Anesthesia

Moderately slow induction can usually be accomplished in the "average" adult by injection of 50 to 75 mg (2 to 3 mL of a 2.5% solution) at intervals of 20 to 40 seconds, depending on the reaction of the patient. Once anesthesia is established, additional injections of 25 to 50 mg can be given whenever the patient moves.

Slow injection is recommended to minimize respiratory depression and the possibility of overdosage. The smallest dose consistent with attaining the surgical objective is the desired goal. Momentary apnea following each injection is typical, and progressive decrease in the amplitude of respiration appears with increasing dosage. Pulse remains normal or increases slightly and returns to normal. Blood pressure usually falls slightly but returns toward normal. Muscles usually relax about 30 seconds after unconsciousness is attained, but this may be masked if a skeletal muscle relaxant is used. The tone of jaw muscles is a fairly reliable index. The pupils may dilate but later contract; sensitivity to light is not usually lost until a level of anesthesia deep enough to permit surgery is attained. Nystagmus and divergent strabismus are characteristic during early stages, but at the level of surgical anesthesia, the eyes are central and fixed. Corneal and conjunctival reflexes disappear during surgical anesthesia.

When Pentothal (Thiopental Sodium for Injection, USP) is used for induction in balanced anesthesia with a skeletal muscle relaxant and an inhalation agent, the total dose of Pentothal can be estimated and then injected in two to four fractional doses. With this technique, brief periods of apnea may occur which may require assisted or controlled pulmonary ventilation. As an initial dose, 210 to 280 mg (3 to 4 mg/kg) of Pentothal is usually required for rapid induction in the average adult (70 kg).

When Pentothal (Thiopental Sodium for Injection, USP) is used as the sole anesthetic agent, the desired level of anesthesia can be maintained by injection of small repeated doses as needed or by using a continuous intravenous drip in a 0.2% or 0.4% concentration. (Sterile water should not be used as the diluent in these concentrations, since hemolysis will occur.) With continuous drip, the depth of anesthesia is controlled by adjusting the rate of infusion.

Use in Convulsive States

For the control of convulsive status following anesthesia (inhalation or local) or other causes, 75 to 125 mg (3 to 5 mL of a 2.5% solution) should be given as soon as possible after the convulsion begins. Convulsions following the use of a local anesthetic may require 125 to 250 mg of Pentothal given over a ten minute period, if the convulsion is caused by a local anesthetic, the required dose of Pentothal will depend upon the amount of local anesthetic given and its convulsant properties.

Use in Neurosurgical Patients with Increased Intracranial Pressure

In neurosurgical patients, intermittent bolus injections of 1.5 to 3.5 mg/kg of body weight may be given to reduce intraoperative elevations of intracranial pressure, if adequate ventilation is provided.

Use in Psychiatric Disorders

For narcoanalysis and narcosynthesis in psychiatric disorders, premedication with an antiallergic agent may precede administration of Pentothal. After a test dose, Pentothal (Thiopental Sodium for Injection, USP) is injected at a slow rate of 100 mg/min (4 mL/min of a 2.5% solution) with the patient counting backwards from 100. Shortly after counting becomes confused but before actual sleep is produced, the injection is discontinued. Allow the patient to return to a semidrowsy state where conversation is coherent. Alternatively, Pentothal may be administered by rapid I.V. drip using a 0.2% concentration in 5% dextrose and water. At this concentration, the rate of administration should not exceed 50 mL/min.

MANAGEMENT OF SOME COMPLICATIONS

Respiratory depression (hypoventilation, apnea), which may result from either unusual responsiveness to Pentothal or overdosage, is managed as stated above. Pentothal should be considered to have the same potential for producing respiratory depression as an inhalation agent, and patency of the airway must be protected at all times.

Laryngospasm may occur with light Pentothal narcosis at intubation, or in the absence of intubation if foreign matter or secretions in the respiratory tract create irritation. Laryngeal and bronchial vagal reflexes can be suppressed, and secretions minimized by giving atropine or scopolamine premedication and a barbiturate or opiate. Use of a skeletal muscle relaxant or positive pressure oxygen will usually relieve laryngospasm. Tracheostomy may be indicated in difficult cases.

Myocardial depression (proportional to the amount of drug in direct contact with the heart, can occur and may cause hypotension, particularly in patients with an unhealthy myocardium. Arrhythmias may appear if PCO_2 is elevated, but they are uncommon with adequate ventilation. Management of myocardial depression is the same as for overdosage. Pentothal (Thiopental Sodium for Injection, USP) does not sensitize the heart to epinephrine or other sympathomimetic amines.

Extravascular Infiltration should be avoided. Care should be taken to insure that the needle is within the lumen of the vein before injection of Pentothal. Extravascular injection may cause chemical irritation of the tissues varying from slight tenderness to venospasm, extravasation necrosis and sloughing. This is due primarily to the high alkaline pH (10 to 11) of clinical concentrations of the drug. If extravasation occurs, the local irritant effects can be reduced by injection of 1% procaine locally to relieve pain and enhance vasodilatation. Local application of heat also may help to increase local circulation and removal of the infiltrate.

Intra-arterial injection can occur inadvertently, especially if an aberrant superficial artery is present at the medial aspect of the antecubital fossa. The area selected for intravenous injection of the drug should be palpated for detection of an underlying pulsating vessel. Accidental intra-arterial injection can cause anesthesia and severe pain along the course of the artery with blanching of the arm and fingers. Appropriate corrective measures should be instituted promptly to avoid possible development of gangrene. Any patient exceptional pain warrants stopping the injection. Methods suggested for dealing with this complication vary with the severity of symptoms. The following have been suggested:

1. Dilute the injected Pentothal (Thiopental Sodium for Injection, USP) by removing the tourniquet and any restrictive garments.
2. Leave the needle in place, if possible.
3. Inject the artery with a dilute solution of papaverine, 40 to 80 mg, or 10 mL of 1% procaine, to inhibit smooth muscle spasm.
4. If necessary, perform sympathetic block of the brachial plexus and/or stellate ganglion to relieve pain and assist in opening collateral circulation. Heparin can be injected into the subclavian artery, if desired.
5. Unless otherwise contraindicated, institute immediate heparinization to prevent thrombus formation.
6. Consider local infiltration of an alpha-adrenergic blocking agent such as phentolamine into the vasospastic area.
7. Provide additional symptomatic treatment as required.

Shivering after Pentothal anesthesia, manifested by twitching face muscles and occasional progressive tremors of the arms, head, shoulder and body, is a frequent reaction due to increased sensitivity to cold. Shivering appears if the room environment is cold and if a long vasodilatory heat loss has been assisted with inhalant inhalation anesthesia employing nitrous oxide. Treatment consists of warming the patient with blankets, maintaining room temperature near 27° C (72° F), and administration of chlorpromazine or methylphenidate.

PREPARATION OF SOLUTIONS

Pentothal (Thiopental Sodium for Injection, USP) is supplied as a yellowish, hygroscopic powder in a variety of different containers. Solutions should be prepared aseptically with one of the three following diluents: Sterile Water for Injection, USP, 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. Clinical concentrations used in intermittent intravenous administration vary between 2.0% and 5.0%. A 2.5% or 2.5% solution is most commonly used. 0.4% concentration in sterile water for injection is used; concentrations less than 2.5% in this diluent are not used because they cause hemolysis. For continuous intravenous drip administration, concentrations of 0.2% or 0.4% are used. Solutions may be prepared by adding Pentothal to 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection USP or Normosol®-R pH 7.4.

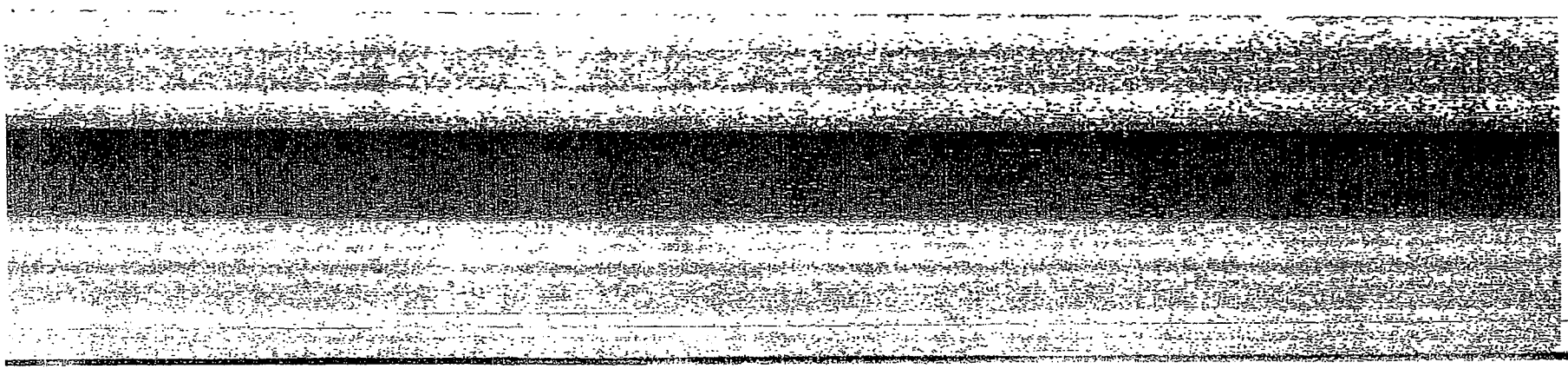
Since Pentothal contains no added bacteriostatic agent, extreme care in preparation and handling should be exercised at all times to prevent the introduction of microbial contaminants. Solutions should be freshly prepared as used promptly; when reconstituted for administration of several patients, unused portions should be discarded after 24 hours. Sterilization by heating should not be attempted.

WARNING: The 2.5 g and larger sizes contain adequate medication for several patients.

COMPATIBILITY

Any solution of Pentothal (Thiopental Sodium for Injection USP) with a visible precipitate should not be administered. The stability of Pentothal solutions depends upon several factors, including the diluent, temperature of storage and the amount of carbon dioxide from room air that gains access to the solution. Any factor or condition which tends to lower pH (increase acidity) of Pentothal solutions will increase the likelihood of precipitation of thiopental acid. Such factors include the use of diluents which are too acid and the absorption of carbon dioxide which can combine with water to form carbonic acid.

Solutions of succinylcholine, tubocurarine or other drugs which have an acid pH should not be mixed with Pentothal solutions. The most stable solutions are those reconstituted in water or isotonic saline, kept under refrigeration and tightly stoppered. The presence or absence of a visible precipitate offers a practical guide to the physical compatibility of prepared solutions of Pentothal.



rarely, vein irritation. Rate of administration should be adjusted according to tolerance.

Reactions reported with the use of potassium-containing solutions include nausea, vomiting, abdominal pain and diarrhea. The signs and symptoms of potassium intoxication include paresthesias of the extremities, areflexia, muscular or respiratory paralysis, mental confusion, weakness, hypotension, cardiac arrhythmias, heart block, electrocardiographic abnormalities and cardiac arrest. Potassium deficits result in disruption of neuromuscular function, and intestinal ileus and flatation.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

VERDOSAGE

the event of fluid overload during parenteral therapy, re-evaluate the ient's condition, and institute appropriate corrective treatment.

In the event of overdosage with potassium-containing solutions, scontinue the infusion immediately, and institute corrective therapy to duce serum potassium levels.

eatment of hyperkalemia includes the following:

Dextrose Injection USP, 10% or 25%, containing 10 units of crystalline insulin per 20 grams of dextrose administered intravenously, at a rate of 300 to 500 mL per hour.

Absorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally and as retention enema.

Hemodialysis and peritoneal dialysis. The use of potassium-containing

foods or medications must be eliminated. However, in cases of digitalization, too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

DOSAGE AND ADMINISTRATION

Potassium Chloride for Injection Concentrate, USP must be diluted before administration. Care must be taken to ensure there is complete mixing of the potassium chloride with the large volume fluid, particularly if soft or bag type containers are used.

The dose and rate of administration are dependent upon the specific condition of each patient.

If the serum potassium level is greater than 2.5 mEq/liter, potassium can be given at a rate not to exceed 10 mEq/hour in a concentration of up to 40 mEq/liter. The 24-hour total dose should not exceed 200 mEq.

If urgent treatment is indicated (serum potassium level less than 2.0 mEq/liter with electrocardiographic changes and/or muscle paralysis) potassium chloride may be infused very cautiously at a rate of up to 40 mEq/hour. In such cases, continuous cardiac monitoring is essential. As much as 400 mEq may be administered in a 24 hour period. In critical conditions, potassium chloride may be administered in saline (unless contraindicated), rather than in dextrose containing fluids, as dextrose may lower serum potassium levels.

Prior to entering vial, remove the metal seal and cleanse the rubber closure with a suitable antiseptic agent.

Parenteral drug products should be inspected visually for particulate matter and discoloration, whenever solution and container permit.

TO PREVENT NEEDLE-STICK INJURIES, NEEDLES SHOULD NOT BE RECAPPED, PURPOSELY BENT, OR BROKEN BY HAND.

HOW SUPPLIED

Potassium Chloride for Injection Concentrate, USP, is supplied in single-dose containers as follows:

List No.	Type Container	Concentration
3507	Glass Ampuls	20 mEq/10 mL
3934	Glass Ampuls	40 mEq/20 mL
4931	Glass Pintop Vials	10 mEq/5 mL
1498	Glass Pressurized Pintop Vials	30 mEq/15 mL
1499	Glass Pressurized Pintop Vials	40 mEq/20 mL
8636	Glass Fliptop Vials	10 mEq/5 mL
4932	Plastic Pintop Vials	20 mEq/10 mL
8637	Plastic Fliptop Vials	20 mEq/10 mL
8638	Plastic Fliptop Vials	30 mEq/15 mL
8653	Plastic Fliptop Vials	40 mEq/20 mL

Store at controlled room temperature 15° to 30°C (59° to 86°F) [See USP]

Revised: April, 2004

HOSPIRA, INC., LAKE FOREST, IL 60045 USA

Hospira

POTASSIUM CHLORIDE
for Injection Concentrate, USP

℞ only

CONCENTRATE

MUST BE DILUTED BEFORE USE

FOR INTRAVENOUS INFUSION ONLY; MUST BE DILUTED PRIOR TO INJECTION.

Ampuls
Flip-Top Vials
Pintop Vials
Pressurized Pintop Vials

EN-0069

SCRIPTION

assium Chloride for Injection Concentrate, USP, is a sterile, pyrogenic, concentrated solution of potassium chloride, USP in water injection administered by intravenous infusion only after dilution in a ir volume of fluid. They are provided in the following variety of centrations and sizes comprising a choice of single-dose containers, all ned to provide the commonly prescribed amounts of potassium ride for single-dose infusion after dilution in suitable large volume ersels

Size Solution* (mL & size)	K+ mEq/mL	KCl mg/mL	mOsmol/mL (calc.)
2 mEq/20 mL	1	112	2
2 mEq/5mL	2	149	4
2 mEq/10 mL	2	149	4
2 mEq/15 mL	2	149	4
2 mEq/20 mL	2	149	4

contain hydrochloric acid for pH adjustment.

solutions contain no bacteriostat, antimicrobial agent or added (except for pH adjustment) and each is intended only for single-dose on latter dilution. When smaller doses are required, discard the n portion. The pH is 4.5 (4.0 to 8.0).

ssium Chloride for Injection Concentrate, USP (approximately 0.1mEq ental fluid and electrolyte replenisher.

ssium Chloride, USP is chemically designated KCl, a white granular freely soluble in water.

semi-rigid material used for the plastic vials is fabricated from a

specially formulated polyolefin. It is a copolymer of ethylene and propylene. The safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers. The container requires no vapor barrier to maintain the proper drug concentration.

CLINICAL PHARMACOLOGY

Potassium is the chief cation of body cells (150 mEq/liter of intracellular water) and is concerned with the maintenance of body fluid composition and electrolyte balance. Potassium participates in carbohydrate utilization and protein synthesis, and is critical in the regulation of nerve conduction and muscle contraction, particularly in the heart. Chloride, the major extracellular anion, closely follows the metabolism of sodium, and changes in the acid-base balance of the body are reflected by changes in the chloride concentration.

Normally about 80 to 90% of the potassium intake is excreted in the urine, the remainder in the stools and, to a small extent, in perspiration. The kidney does not conserve potassium well so that during fasting, or in patients on a potassium-free diet, potassium loss from the body continues, resulting in potassium depletion. A deficiency of either potassium or chloride will lead to a deficit of the other.

INDICATIONS AND USAGE

Potassium Chloride for Injection Concentrate, USP is indicated in the treatment of potassium deficiency states when oral replacement is not feasible.

CONTRAINDICATIONS

Potassium Chloride for Injection Concentrate, USP is contraindicated in diseases where high potassium levels may be encountered, and in patients with hyperkalemia, renal failure and in conditions in which potassium

retention is present.

WARNINGS

To avoid potassium intoxication, do not infuse solutions rapidly. In patients with severe renal insufficiency, administration of potassium chloride may cause potassium intoxication and life threatening hyperkalemia.

The administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema.

The risk of dilutional states is inversely proportional to the electrolyte concentration. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentration.

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

General

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the

condition of the patient warrants such evaluation. Significant deviation from normal concentrations may require the use of additional electrolyte supplements, or the use of electrolyte-free dextrose solutions to which individualized electrolyte supplements may be added.

Potassium therapy should be guided primarily by serial electrocardiograms, especially in patients receiving digitalis. Serum potassium levels are not necessarily indicative of tissue potassium level. Solutions containing potassium should be used with caution in the presence of cardiac disease, particularly in the presence of renal disease and in such instances, cardiac monitoring is recommended.

Solutions containing dextrose should be used with caution in patients with overt or known subclinical diabetes mellitus, or carbohydrate intolerance for any reason.

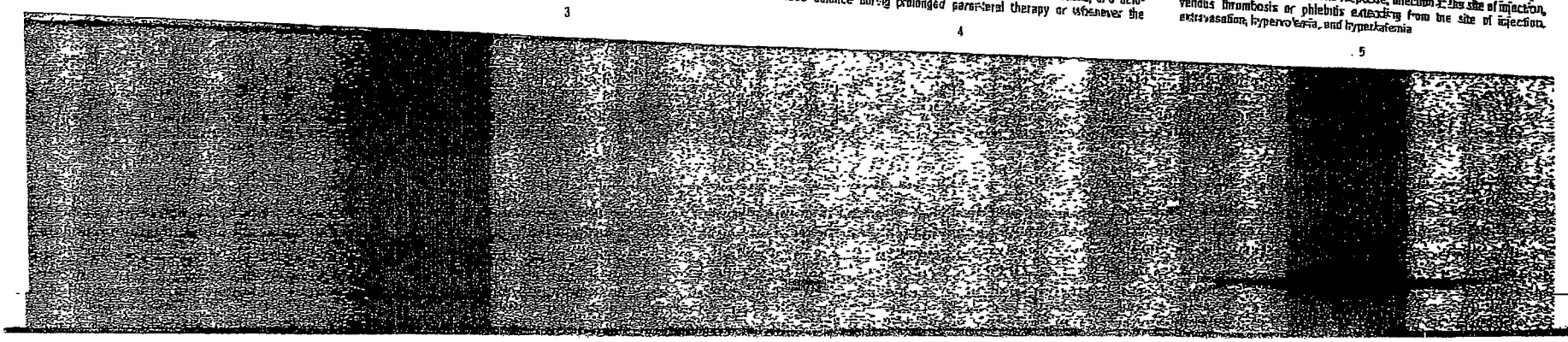
If the administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Pregnancy

Teratogenic Effects: Pregnancy category C. Animal reproduction studies have not been conducted with potassium chloride. It is also not known whether potassium chloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Potassium chloride should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation, hypervolemia, and hyperkalemia



0236

Pancuronium Bromide Injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

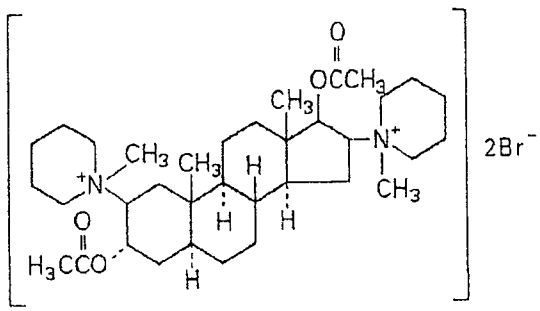
1 mg/mL Fliptop Vial

R_x only

DESCRIPTION

Pancuronium Bromide is a nondepolarizing neuromuscular blocking agent chemically designated as the aminosteroid 2β, 16β - dipiperidino-5α-androstane-3α, 17-β diol diacetate dimethobromide, $C_{35}H_{60}Br_2N_2O_4$. It is a fine white odorless powder which is soluble in water, alcohol and chloroform.

It has the following structural formula:



Pancuronium Bromide Injection is available in sterile, isotonic, nonpyrogenic solution for injection. Each mL contains pancuronium bromide 1 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 is 4.0 (3.8 to 4.2).

CLINICAL PHARMACOLOGY

Pancuronium bromide 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 bromide is approximately 1/3 less potent than vecuronium and approximately 5 times as potent as d-tubocurarine: the duration of neuromuscular blockage produced by pancuronium bromide is longer than that of vecuronium at initially equipotent doses.

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 use of a peripheral nerve stimulator is of benefit in assessing the degree of neuromuscular blockade.

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.

Data on histamine assays and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are rare. (See *ADVERSE REACTIONS*).

Pharmacokinetics

The elimination half-life of pancuronium has been reported to range between 89-161 minutes. The volume of distribution ranges from 241-280 mL/kg; and plasma clearance is approximately 1.1–1.9 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 of neuromuscular blockade, as determined by peripheral nerve stimulation is variable and sometimes very much slower than normal.

INDICATIONS AND USAGE

Pancuronium bromide is indicated as an adjunct to general anesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS

Pancuronium Bromide Injection is contraindicated in patients known to be hypersensitive to the drug.

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 bromide may have profound effects. 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.

Benzyl alcohol has been reported to be associated with a fatal "gasping syndrome" in premature infants.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to those received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including pancuronium) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of pancuronium bromide for preterm and term infants includes amounts of benzyl alcohol well below that associated with toxicity; however, the amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources.

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 Bromide Injection 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 is selected, for other reasons, to be used in a patient with renal failure.

Altered Circulation Time

Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore, dosage should not be increased.

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**).

Long-term Use in I.C.U.

In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance, and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered.

Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

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 bromide.

CNS

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

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 bromide, the administration of pancuronium bromide should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade.

If a small dose of pancuronium bromide is given at least 3 minutes prior to the administration of succinylcholine, in order to reduce the incidence and intensity of succinylcholine-induced fasciculations, 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 bromide. The combination of pancuronium bromide-metocurine and pancuronium bromide-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 bromide will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents, the intubating dose of pancuronium bromide 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 bromide, 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 bromide.

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.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: ***Pregnancy Category C***

Animal reproduction studies have not been performed. It is not known whether pancuronium bromide can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pancuronium bromide should be given to a pregnant woman only if the administering clinician decides that the benefits outweigh the risks.

Pancuronium bromide may be used in operative obstetrics (**Caesarean 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.

Pediatric Use

Dose response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Neonates are especially sensitive to nondepolarizing neuromuscular blocking agents, such as pancuronium bromide, during the first month of life. It is recommended that a test dose of 0.02 mg/kg be given first in this group to measure responsiveness.

The prolonged use of pancuronium bromide 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 between the combined use of these drugs and the reported cases of methemoglobinemia has not been established.

ADVERSE REACTIONS

Neuromuscular

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. (See ***PRECAUTIONS:*** **Pediatric Use**).

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

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit.

Cardiovascular

See discussion of circulatory effects in *CLINICAL PHARMACOLOGY.*

Gastrointestinal

Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin

An occasional transient rash is noted accompanying the use of pancuronium bromide.

Other

Although histamine release is not a characteristic action of pancuronium bromide, rare hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia and other reactions possibly mediated by histamine release have been reported.

OVERDOSAGE

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

Excessive doses of pancuronium bromide can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed may occur with pancuronium bromide 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 help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Pyridostigmine bromide, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate, will usually antagonize the skeletal muscle relaxant action of pancuronium bromide. 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. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION

Pancuronium Bromide Injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only. Since potent inhalational anesthetics or prior use of succinylcholine may enhance the intensity and duration of pancuronium bromide (see ***PRECAUTIONS:*** **Drug Interactions**), the lower end of the recommended initial dosage range may suffice when pancuronium bromide is first used after intubation with succinylcholine and/or after maintenance doses of volatile liquid inhalational anesthetics are started. To obtain maximum clinical benefits of Pancuronium Bromide Injection and to minimize the possibility of overdosage, the monitoring of muscle twitch response to a peripheral nerve stimulator is advised.

In adults under balanced anesthesia the initial intravenous dosage range is 0.04 to 0.1 mg/kg. Later incremental doses starting at 0.01 mg/kg may be used. These increments slightly increase the magnitude of the blockade and significantly increase the duration of blockade because a significant number of myoneural junctions are still blocked when there is clinical need for more drug.

If Pancuronium Bromide Injection is used to provide skeletal muscle relaxation for endotracheal intubation, a bolus dose of 0.06 to 0.1 mg/kg is recommended. Conditions satisfactory for intubation are usually present within 2 to 3 minutes (see ***PRECAUTIONS***).

Dosage in Children

Dose response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Neonates are especially sensitive to nondepolarizing neuromuscular blocking agents, such as Pancuronium Bromide Injection, during the first month of life. It is recommended that a test dose of 0.02 mg/kg be given first in this group to measure responsiveness.

Caesarean 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 (see ***PRECAUTIONS:*** **Drug Interactions**), is the same as for general surgical procedures.

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

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

When mixed with the above solutions in glass or plastic containers, Pancuronium Bromide Injection will remain stable in solution for 48 hours with no alteration in potency or pH; no decomposition is observed and there is no absorption to either the glass or plastic container.

HOW SUPPLIED

Pancuronium Bromide Injection is supplied as follows:

List No.		Container
4646	Multiple-dose	10 mL Fliptop Vial—1 mg/mL cartons of 25

STORAGE

Store in refrigerator 2° to 8°C (36° to 46°F).

The 10mL vial will maintain full clinical potency for up to six months at room temperature.

Revised: November, 2004

Hospira

 EN-0548 Printed in USA

HOSPIRA, INC., LAKE FOREST, IL 60045 USA

CALCULATIONS FOR VARIOUS CONCENTRATIONS

Concentration Desired		Amounts to Use	
Percent	mg/mL	Pentothal g	Diluent mL
0.2	2	1	500
0.4	4	1	250
		2	500
2.0	20	5	250
		10	500
2.5	25	1	40
		5	200
5	50	1	20
		5	100

Reconstituted solutions of Pentothal (Thiopental Sodium Injection, USP) should be inspected visually for particu- matter and discoloration, whenever solution and con- ter permit.

W SUPPLIED

ntothal is available in a variety of sizes and containers wn at the end of this insert.

luents in
ntothal® Kits

ADY-TO-MIX SYRINGES AND VIALS

r preparing solutions of Thiopental Sodium Injection, USP)

SCRIPTION

following diluents in various container, syringe and vial as are provided in Pentothal Kits. Pentothal Ready-to-Mix inges and Vials for preparing solutions of Pentothal iopental Sodium for Injection, USP) for clinical use:

Sterile Water for Injection, USP is a sterile, nonpyrogenic paration of water for injection which contains no eteriostat, antimicrobial agents or added buffers. The pH 5.7 (5.0 to 7.0).

Sterile Water for Injection, USP is a pharmaceutic aid lvent) for intravenous administration only after addition of olute.

Water is chemically designated H_2O

0.9% Sodium Chloride Injection, USP is a sterile, npyrogenic, isotonic solution of sodium chloride and water injection Each mL contains sodium chloride 9 mg (308 ismol/liter calc). It contains no bacteriostat, antimicrobial ents or added buffers except for pH adjustment. May ntain hydrochloric acid and/or sodium hydroxide for pH justment. pH is 5.7 (4.5 to 7.0).

0.9% Sodium Chloride Injection, USP is an isotonic vehicle intravenous administration of another solute.

Sodium chloride is chemically designated NaCl, a white rystalline compound freely soluble in water.

The semi-rigid vial contained in List Nos. 3329, 6418, 6419, 20 and 6435 is fabricated from a specially formulated lyolefin. It is a copolymer of ethylene and propylene. The fety of the plastic has been confirmed by tests in animals cording to USP biological standards for plastic ntainers. The container requires no vapor barrier to intain the proper labeled volume.

INICAL PHARMACOLOGY

erile Water for Injection, USP serves only as a pharmaceutic l for diluting or dissolving drugs prior to administration.

Water is an essential constituent of all body tissues and counts for approximately 70% of total body weight. erage normal adult daily requirement ranges from two to ree liters (1.0 to 1.5 liters each for insensible water loss by rspiration and urine excretion).

Water balance is maintained by various regulatory mechanisms. Water distribution depends primarily on the concentration of dissociated electrolytes in the body compartments and sodium (Na^+) plays a major role in maintaining a physiologic equilibrium between fluid intake and output.

0.9% Sodium Chloride Injection, USP serves only as an isotonic vehicle for drugs prior to administration.

Sodium chloride in water is an electrolyte solution of sodium (Na^+) and chloride (Cl^-) ions. These ions are normal constituents of the body fluids (principally extracellular) and are essential for maintaining electrolyte balance.

The distribution and excretion of sodium (Na^+) and chloride (Cl^-) are largely under the control of the kidney which maintains a balance between intake and output of these ions.

The small volumes of fluid and amounts of sodium chloride provided by 0.9% Sodium Chloride Injection in Ready-to-Mix Syringes are unlikely to produce a significant effect on fluid or electrolyte balance.

INDICATIONS AND USAGE

These products are indicated only for preparing Pentothal (Thiopental Sodium for Injection, USP) solutions for clinical use.

CONTRAINDICATIONS

Do not use unless the diluent is clear and the bottle or vial seal or syringe package is undamaged.

Diluents in Pentothal Kits, Ready-to-Mix Syringes or Vials should not be used for fluid or sodium chloride replacement.

WARNINGS

Intravenous administration of Sterile Water for Injection, USP without a solute may result in hemolysis.

Use aseptic technique for preparing Pentothal solutions when using Pentothal Kits, Syringes or Vials and during withdrawal from reconstituted single or multiple-use containers.

Administer only clear reconstituted solutions.

Use within 24 hours after reconstitution. Discard unused portions.

PRECAUTIONS

Do not use unless solution is clear and container is undamaged.

Inspect reconstituted (mixed) solutions of Pentothal (Thiopental Sodium for Injection, USP) for clarity and freedom from precipitation or discoloration prior to administration. Use reconstituted solution only if it is clear, free from precipitate and not discolored.

Use Transfer Label in each Pentothal Kit and affix to container of reconstituted solution to show concentration and time of preparation.

Pregnancy Category C. Animal reproduction studies have not been conducted with sterile water for injection or sodium chloride injection. It is also not known whether sterile water or sodium chloride injection containing additives can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sterile water for injection or sodium chloride injection with additives should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Reactions which may occur because of the diluents, technique of preparation or mixing, or administration of reconstituted solutions of Pentothal include febrile response or infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection and extravasation.

If an adverse reaction does occur, discontinue the injection, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of unused solution (or the used container or syringe) for examination if deemed necessary.

DRUG ABUSE AND DEPENDENCE

None known.

OVERDOSAGE

Used as diluents for preparing solutions of Pentothal (Thiopental Sodium for Injection, USP) the small volumes of administered fluid (from Sterile Water for Injection in bottles and vials) and amounts of sodium chloride (from 0.9% Sodium Chloride Injection in Ready-to-Mix Syringes) are unlikely to pose a threat of fluid or sodium chloride overload.

DOSAGE AND ADMINISTRATION

Pentothal solutions should be administered only by intravenous injection and by individuals experienced in the conduct of intravenous anesthesia.

The volume and choice of diluent for preparing Pentothal (Thiopental Sodium for Injection, USP) solutions for clinical use depends on the concentration and vehicle desired. Pentothal Kits provide only Sterile Water for Injection as the diluent for individual or multi-patient use; Pentothal Ready-to-Mix Syringes provide only 0.9% Sodium Chloride Injection, USP as the diluent for individual patient use; vials provide only Sterile Water for Injection, USP as the diluent for individual patient use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See PRECAUTIONS.

HOW SUPPLIED

The diluent in Pentothal Kits is supplied in various size containers with various dosage sizes of Pentothal (Thiopental Sodium for Injection, USP). Kits include all items needed for aseptic transfer of Pentothal powder from a squeeze bottle into the diluent container.

The diluent in Pentothal Ready-to-Mix Syringes is supplied in a separate container to permit mixing with the Pentothal in a powder vial to permit immediate intravenous injection of reconstituted solution into a vein or attachment to a standard stopcock assembly.

Vials are supplied in cartons with different dosage sizes of Pentothal for preparing 2.0% or 2.5% concentrations by using a separate syringe (not supplied) for mixing.

See table for list of sizes available.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Keep reconstituted solution in a cool place.

Caution: Federal (USA) law prohibits dispensing without prescription.

Table: Pentothal® (Thiopental Sodium for Injection, USP) and Diluent in Kits, Ready-to-Mix Syringes and Ready-to-Mix LifeShield* Syringes

List No.	Pentothal	Pentothal Container	Diluent (mL)*	Diluent Container	Theoretical Reconstituted Conc.
6259 (Kit)	2.5 g	Squeeze Bottle	W (125)	PF Bottle	2% (20 mg/mL)
6108 (Kit)	5 g	Squeeze Bottle	W (250)	PF Bottle	2% (20 mg/mL)
6244 (Kit)	1 g	Squeeze Bottle	W (40)	PF Bottle	2.5% (25 mg/mL)
6260 (Kit)	2.5 g	Squeeze Bottle	W (100)	PF Bottle	2.5% (25 mg/mL)
6504 (Kit)	5 g	Squeeze Bottle	W (200)	Bottle	2.5% (25 mg/mL)
6435 (Kit)	1 g	Vial	W (50)	Plastic Vial	2% (20 mg/mL)
3329 (Kit)	500 mg	Vial	W (20)	Plastic Vial	2.5% (25 mg/mL)
9087 (Kit)	1 g	Vial	W (50)	Plastic Vial	2% (20 mg/mL)
9089 (Kit)	500 mg	Vial	W (20)	Plastic Vial	2.5% (25 mg/mL)
6246 (Ready-to-Mix Syringe)	400 mg	Syringe	S (20)	Syringe	2% (20 mg/mL)
6241 (Ready-to-Mix Syringe)	250 mg	Syringe	S (10)	Syringe	2.5% (25 mg/mL)
6243 (Ready-to-Mix Syringe)	500 mg	Syringe	S (20)	Syringe	2.5% (25 mg/mL)
3351 (Ready-to-Mix LifeShield Syringe)	250 mg	Syringe	S (10)	Plastic Vial	2.5% (25 mg/mL)
3352 (Ready-to-Mix LifeShield Syringe)	400 mg	Syringe	S (20)	Plastic Vial	2% (20 mg/mL)
3353 (Ready-to-Mix LifeShield Syringe)	500 mg	Syringe	S (20)	Plastic Vial	2.5% (25 mg/mL)
6418 (Ready-to-Mix Syringe)	250 mg	Syringe	W (10)	Plastic Vial	2.5% (25 mg/mL)
6419 (Ready-to-Mix Syringe)	400 mg	Syringe	W (20)	Plastic Vial	2% (20 mg/mL)
6420 (Ready-to-Mix Syringe)	500 mg	Syringe	W (20)	Plastic Vial	2.5% (25 mg/mL)

PF — denotes Partial-Fill
W — denotes Sterile Water for Injection, USP
S — denotes 0.9% Sodium Chloride Injection, USP

* Diluent containers are slightly overfilled to assure compliance with USP minimum fill volume requirements.

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ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

PENTOTHAL®

THIOPENTAL SODIUM FOR INJECTION, USP

III

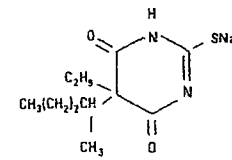
WARNING: MAY BE HABIT FORMING.

DESCRIPTION

Pentothal (Thiopental Sodium for Injection, USP) is a thiol
biturate, the sulfur analogue of sodium pentobarbital.

The drug is prepared as a sterile powder and after rec
stitution with an appropriate diluent is administered by
intravenous route.

Pentothal is chemically designated sodium 5-ethyl-5
methylbutyl)-2-thiobarbiturate and has the following st
tural formula:



The drug is a yellowish, hygroscopic powder, stabi
with anhydrous sodium carbonate as a buffer (60 mg
thiopental sodium).

CLINICAL PHARMACOLOGY

Pentothal (Thiopental Sodium for Injection, USP) i
ultrashort-acting depressant of the central nervous sy
which induces hypnosis and anesthesia, but not analge
produces hypnosis within 30 to 40 seconds of intrave
injection. Recovery after a small dose is rapid, with
somnolence and retrograde amnesia. Repeated introve
doses lead to prolonged anesthesia because fatty tis
act as a reservoir; they accumulate Pentoth
concentrations 6 to 12 times greater than the pl
concentration, and then release the drug slowly to
prolonged anesthesia.

The half-life of the elimination phase after a s
intravenous dose is three to eight hours.

The distribution and fate of Pentothal (as with
barbiturates) is influenced chiefly by its lipid sol
(partition coefficient), protein binding and exte
ionization. Pentothal has a partition coefficient of 580.

Approximately 80% of the drug in the blood is bou
plasma protein. Pentothal is largely degraded in the liv
to a smaller extent in other tissues, especially the kidne
brain. It has a pK_a of 7.4.

Concentration in spinal fluid is slightly less than
plasma.

Biotransformation products of thiopental are ph
cologically inactive and mostly excreted in the urine.

0245

Pentothal

DICATIONS AND USAGE

ntothal (Thiopental Sodium for Injection, USP) is indicated as the sole anesthetic agent for brief (15 minute) rocedures, (2) for induction of anesthesia prior to ministration of other anesthetic agents, (3) to supplement tional anesthesia, (4) to provide hypnosis during balanced esthesia with other agents (or analgesia or muscle axation, (5) for the control of convulsive states during or owing inhalation anesthesia, local anesthesia, or other ses, (6) in neurosurgical patients with increased cranial pressure, if adequate ventilation is provided, d (7) for narcoanalysis and narcosynthesis in psychiatric orders.

NTRAINDICATIONS

solute Contraindications:

Absence of suitable veins for intravenous administration, hypersensitivity (allergy) to barbiturates and (3) variegate rphyria (South African) or acute intermittent porphyria.

lative Contraindications:

Severe cardiovascular disease, (2) hypotension or shock, conditions in which the hypnotic effect may be prolonged potentiated — excessive premedication, Addison's ease, hepatic or renal dysfunction, myxedema, increased od urea, severe anemia, asthma, myasthenia gravis, and status asthmaticus.

ARNINGS

EP RESUSCITATIVE AND ENDOTRACHEAL INTUBATION UIPMENT AND OXYGEN READILY AVAILABLE. AINTAIN PATENCY OF THE AIRWAY AT ALL TIMES.

This drug should be administered only by persons ilified in the use of intravenous anesthetics.

Avoid extravasation or intra-arterial injection.

ARNING: MAY BE HABIT FORMING.

ECAUTIONS

serve aseptic precautions at all times in preparation and idling of Pentothal (Thiopental Sodium for Injection, USP) utions.

f used in conditions involving relative contraindications, uce dosage and administer slowly.

Care should be taken in administering the drug to patients h advanced cardiac disease, increased intracranial ssure, ophthalmoplegia plus, asthma, myasthenia gravis l endocrine insufficiency (pituitary, thyroid, adrenal, ncreas).

Drug Interactions. The following drug interactions have en reported with thiopental.

Drug	Effect
Probenecid	Prolonged action of thiopental
Diazoxide	Hypotension
Zimeldine	Thiopental antagonism
Opioid analgesics	Decreased antinociceptive action
Aminophylline	Thiopental antagonism
Midazolam	Synergism

Nursing Mothers. Thiopental sodium readily crosses the ental barrier and small amounts may appear in the milk ursing mothers following administration of large doses.

Pregnancy Category C. Animal reproduction studies have been conducted with Pentothal. It is also not known ether Pentothal can cause fetal harm when administered to regnant woman or can affect reproduction capacity. ntothal should be given to a pregnant woman only if clearly ded.

ADVERSE REACTIONS

Adverse reactions include respiratory depression, myocardial depression, cardiac arrhythmias, prolonged somnolence and recovery, sneezing, coughing, bronchospasm, laryngospasm and shivering. Anaphylactic and anaphylactoid reactions to Pentothal (Thiopental Sodium for Injection, USP) have been reported. Symptoms, e.g., urticaria, bronchospasm, vasodilation and edema should be managed by conventional means.

Rarely, immune hemolytic anemia with renal failure and radial nerve palsy have been reported.

DRUG ABUSE AND DEPENDENCE

WARNING: MAY BE HABIT FORMING.

Thiopental sodium is classified as a Schedule III controlled substance.

OVERDOSAGE

Overdosage may occur from too rapid or repeated injections. Too rapid injection may be followed by an alarming fall in blood pressure even to shock levels. Apnea, occasional laryngospasm, coughing and other respiratory difficulties with excessive or too rapid injections may occur. In the event of suspected or apparent overdosage, the drug should be discontinued, a patent airway established (intubate if necessary) or maintained, and oxygen should be administered, with assisted ventilation if necessary. The lethal dose of barbiturates varies and cannot be stated with certainty. Lethal blood levels may be as low as 1 mg/100 mL for short-acting barbiturates; less if other depressant drugs or alcohol are also present.

MANAGEMENT OF OVERDOSAGE

It is generally agreed that respiratory depression or arrest due to unusual sensitivity to thiopental sodium or overdosage is easily managed if there is no concomitant respiratory obstruction. If the airway is patent, any method of ventilating the lungs (that prevents hypoxia) should be successful in maintaining other vital functions. Since depression of respiratory activity is one of the characteristic actions of the drug, it is important to observe respiration closely.

Should laryngeal spasm occur, it may be relieved by one of the usual methods, such as the use of a relaxant drug or positive pressure oxygen. Endotracheal intubation may be indicated in difficult cases.

DOSAGE AND ADMINISTRATION

Pentothal is administered by the intravenous route only. Individual response to the drug is so varied that there can be no fixed dosage. The drug should be titrated against patient requirements as governed by age, sex and body weight. Younger patients require relatively larger doses than middle-aged and elderly persons; the latter metabolize the drug more slowly. Pre-puberty requirements are the same for both sexes, but adult females require less than adult males. Dose is usually proportional to body weight and obese patients require a larger dose than relatively lean persons of the same weight.

Premedication

Premedication usually consists of atropine or scopolamine to suppress vagal reflexes and inhibit secretions. In addition, a barbiturate or an opiate is often given. Sodium pentobarbital injection (Nembutal®) is suggested because it provides a preliminary indication of how the patient will react to barbiturate anesthesia. Ideally, the peak effect of these medications should be reached shortly before the time of induction.

Test Dose

It is advisable to inject a small "test" dose of 25 to 75 mg (1 to 3 mL of a 2.5% solution) of Pentothal (Thiopental Sodium for Injection, USP) to assess tolerance or unusual sensitivity to Pentothal, and pausing to observe patient reaction for at least 60 seconds. If unexpectedly deep anesthesia develops or if respiratory depression occurs, consider these possibilities: (1) the patient may be unusually sensitive to Pentothal, (2) the solution may be more concentrated than had been assumed, or (3) the patient may have received too much premedication.

Use in Anesthesia

Moderately slow induction can usually be accomplished in the "average" adult by injection of 50 to 75 mg (2 to 3 mL of a 2.5% solution) at intervals of 20 to 40 seconds, depending on the reaction of the patient. Once anesthesia is established, additional injections of 25 to 50 mg can be given whenever the patient moves.

Slow injection is recommended to minimize respiratory depression and the possibility of overdosage. The smallest dose consistent with attaining the surgical objective is the desired goal. Momentary apnea following each injection is typical, and progressive decrease in the amplitude of respiration appears with increasing dosage. Pulse remains normal or increases slightly and returns to normal. Blood pressure usually falls slightly but returns toward normal. Muscles usually relax about 30 seconds after unconsciousness is attained, but this may be masked if a skeletal muscle relaxant is used. The tone of jaw muscles is a fairly reliable index. The pupils may dilate but later contract; sensitivity to light is not usually lost until a level of anesthesia deep enough to permit surgery is attained. Nystagmus and divergent strabismus are characteristic during early stages, but at the level of surgical anesthesia, the eyes are central and fixed. Corneal and conjunctival reflexes disappear during surgical anesthesia.

When Pentothal (Thiopental Sodium for Injection, USP) is used for induction in balanced anesthesia with a skeletal muscle relaxant and an inhalation agent, the total dose of Pentothal can be estimated and then injected in two to four fractional doses. With this technique, brief periods of apnea may occur which may require assisted or controlled pulmonary ventilation. As an initial dose, 210 to 280 mg (3 to 4 mg/kg) of Pentothal is usually required for rapid induction in the average adult (70 kg).

When Pentothal (Thiopental Sodium for Injection, USP) is used as the sole anesthetic agent, the desired level of anesthesia can be maintained by injection of small repeated doses as needed or by using a continuous intravenous drip in a 0.2% or 0.4% concentration. (Sterile water should not be used as the diluent in these concentrations, since hemolysis will occur.) With continuous drip, the depth of anesthesia is controlled by adjusting the rate of infusion.

Use in Convulsive States

For the control of convulsive states following anesthesia (inhalation or local) or other causes, 75 to 125 mg (3 to 5 mL of a 2.5% solution) should be given as soon as possible after the convulsion begins. Convulsions following the use of a local anesthetic may require 125 to 250 mg of Pentothal given over a ten minute period. If the convulsion is caused by a local anesthetic, the required dose of Pentothal will depend upon the amount of local anesthetic given and its convulsant properties.

Use in Neurosurgical Patients with Increased Intracranial Pressure

In neurosurgical patients, intermittent bolus injections of 1.5 to 3.5 mg/kg of body weight may be given to reduce intraoperative elevations of intracranial pressure, if adequate ventilation is provided.

Use in Psychiatric Disorders

For narcoanalysis and narcosynthesis in psychiatric disorders, premedication with an anticholinergic agent may precede administration of Pentothal. After a test dose, Pentothal (Thiopental Sodium for Injection, USP) is injected at a slow rate of 100 mg/min (4 mL/min of a 2.5% solution) with the patient counting backwards from 100. Shortly after counting becomes confused but before actual sleep is produced, the injection is discontinued. Allow the patient to return to a semidrowsy state where conversation is coherent. Alternatively, Pentothal may be administered by rapid I.V. drip using a 0.2% concentration in 5% dextrose and water. At this concentration, the rate of administration should not exceed 50 mL/min.

MANAGEMENT OF SOME COMPLICATIONS

Respiratory depression (hypoventilation, apnea), which may result from either unusual responsiveness to Pentothal or overdosage, is managed as stated above. Pentothal should be considered to have the same potential for producing respiratory depression as an inhalation agent, and patency of the airway must be protected at all times.

Laryngospasm may occur with light Pentothal narcosis at intubation, or in the absence of intubation if foreign matter or secretions in the respiratory tract create irritation. Laryngeal and bronchial vagal reflexes can be suppressed, and secretions minimized by giving atropine or scopolamine premedication and a barbiturate or opiate. Use of a skeletal muscle relaxant or positive pressure oxygen will usually relieve laryngospasm. Tracheostomy may be indicated in difficult cases.

Myocardial depression, proportional to the amount of drug in direct contact with the heart, can occur and may cause hypotension, particularly in patients with an unhealthy myocardium. Arrhythmias may appear if PCO_2 is elevated, but they are uncommon with adequate ventilation. Management of myocardial depression is the same as for overdosage. Pentothal (Thiopental Sodium for Injection, USP) does not sensitize the heart to epinephrine or other sympathomimetic amines.

Extravascular infiltration should be avoided. Care should be taken to insure that the needle is within the lumen of the vein before injection of Pentothal. Extravascular injection may cause chemical irritation of the tissues varying from slight tenderness to venospasm, extensive necrosis and sloughing. This is due primarily to the high alkaline pH (10 to 11) of clinical concentrations of the drug. If extravasation occurs, the local irritant effects can be reduced by injection of 1% procaine locally to relieve pain and enhance vasodilatation. Local application of heat also may help to increase local circulation and removal of the infiltrate.

Intra-arterial injection can occur inadvertently, especially if an aberrant superficial artery is present at the medial aspect of the antecubital fossa. The area selected for intravenous injection of the drug should be palpated for detection of an underlying pulsating vessel. Accidental intra-arterial injection can cause arteriospasm and severe pain along the course of the artery with blanching of the arm and fingers. Appropriate corrective measures should be instituted promptly to avoid possible development of gangrene. Any patient complaint of pain warrants stopping the injection. Methods suggested for dealing with this complication vary with the severity of symptoms. The following have been suggested:

1. Dilute the injected Pentothal (Thiopental Sodium for Injection, USP) by removing the tourniquet and any restrictive garments.
2. Leave the needle in place, if possible.
3. Inject the artery with a dilute solution of papaverine, 40 to 80 mg, or 10 mL of 1% procaine, to inhibit smooth muscle spasm.

4. If necessary, perform sympathetic block of the brac plexus and/or stellate ganglion to relieve pain and as in opening collateral circulation. Papaverine can injected into the subclavian artery, if desired.
5. Unless otherwise contraindicated, institute immedi heparinization to prevent thrombus formation.
6. Consider local infiltration of an alpha-adrenergic bloc agent such as phentolamine into the vasospastic are
7. Provide additional symptomatic treatment as required

Shivering after Pentothal anesthesia, manifested twitching face muscles and occasional progressiun tremors of the arms, head, shoulder and body, is a ther reaction due to increased sensitivity to cold. Shive appears if the room environment is cold and if a la ventilatory heat loss has been sustained with balan inhalation anesthesia employing nitrous oxide. Treatm consists of warming the patient with blankets, maintair room temperature near 22° C (72° F), and administratio chlorpromazine or methylphenidate.

PREPARATION OF SOLUTIONS

Pentothal (Thiopental Sodium for Injection, USP) is supp as a yellowish, hygroscopic powder in a variety of diffe containers. Solutions should be prepared aseptically v one of the three following diluents: Sterile Water Injection, USP, 0.9% Sodium Chloride Injection, USP 5% Dextrose Injection, USP. Clinical concentrations used intermittent intravenous administration vary between 2 and 5.0%. A 2.0% or 2.5% solution is most commonly use 3.4% concentration in sterile water for injection is isoto concentrations less than 2.0% in this diluent are not u because they cause hemolysis. For continuous intraven drip administration, concentrations of 0.2% or 0.4% are us Solutions may be prepared by adding Pentothal 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injec USP or Normosol®-R pH 7.4.

Since Pentothal contains no added bacteriostatic ag extreme care in preparation and handling should exercised at all times to prevent the introduction of micro contaminants. Solutions should be freshly prepared used promptly; when reconstituted for administratio several patients, unused portions should be discarded a 24 hours. Sterilization by heating should not be attempte

WARNING: The 2.5 g and larger sizes contain adeq medication for several patients.

COMPATIBILITY

Any solution of Pentothal (Thiopental Sodium for injec USP) with a visible precipitate should not be administe The stability of Pentothal solutions depends upon sev factors, including the diluent, temperature of storage the amount of carbon dioxide from room air that g access to the solution. Any factor or condition which le to lower pH (increase acidity) of Pentothal solutions increase the likelihood of precipitation of thiopental s Such factors include the use of diluents which are too ac and the absorption of carbon dioxide which can com with water to form carbonic acid.

Solutions of succinylcholine, tubocurarine or other d which have an acid pH should not be mixed with Pento solutions. The most stable solutions are those reconstit in water or isotonic saline, kept under refrigeration tightly stoppered. The presence or absence of a vis precipitate offers a practical guide to the phys compatibility of prepared solutions of Pentothal.

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too rapid infusion of hypertonic solutions may cause local pain and, rarely, vein irritation. Rate of administration should be adjusted according to tolerance.

Reactions reported with the use of potassium-containing solutions include nausea, vomiting, abdominal pain and diarrhea. The signs and symptoms of potassium intoxication include paresthesias of the extremities, areflexia, muscular or respiratory paralysis, mental confusion, weakness, hypotension, cardiac arrhythmias, heart block, electrocardiographic abnormalities and cardiac arrest. Potassium deficits result in disruption of neuromuscular function, and intestinal ileus and dilatation.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

OVERDOSAGE

In the event of fluid overload during parenteral therapy, re-evaluate the patient's condition, and institute appropriate corrective treatment.

In the event of overdosage with potassium-containing solutions, discontinue the infusion immediately, and institute corrective therapy to reduce serum potassium levels.

Treatment of hyperkalemia includes the following.

1. Dextrose Injection USP, 10% or 25%, containing 10 units of crystalline insulin per 20 grams of dextrose administered intravenously, at a rate of 300 to 500 mL per hour
2. Absorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally and as retention enema.
3. Hemodialysis and peritoneal dialysis. The use of potassium-containing

foods or medications must be eliminated. However, in cases of digitalization, too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

DOSAGE AND ADMINISTRATION

Potassium Chloride for Injection Concentrate, USP must be diluted before administration. Care must be taken to ensure there is complete mixing of the potassium chloride with the large volume fluid, particularly if soft or bag type containers are used.

The dose and rate of administration are dependent upon the specific condition of each patient.

If the serum potassium level is greater than 2.5 mEq/liter, potassium can be given at a rate not to exceed 10 mEq/hour in a concentration of up to 40 mEq/liter. The 24-hour total dose should not exceed 200 mEq.

If urgent treatment is indicated (serum potassium level less than 2.0 mEq/liter with electrocardiographic changes and/or muscle paralysis) potassium chloride may be infused very cautiously at a rate of up to 40 mEq/hour. In such cases, continuous cardiac monitoring is essential. As much as 400 mEq may be administered in a 24 hour period. In critical conditions, potassium chloride may be administered in saline (unless contraindicated), rather than in dextrose containing fluids, as dextrose may lower serum potassium levels.

Prior to entering vial, remove the metal seal and cleanse the rubber closure with a suitable antiseptic agent.

Parenteral drug products should be inspected visually for particulate matter and discoloration, whenever solution and container permit.

TO PREVENT NEEDLE-STICK INJURIES, NEEDLES SHOULD NOT BE RECAPPED, PURPOSELY BENT, OR BROKEN BY HAND.

HOW SUPPLIED

Potassium Chloride for Injection Concentrate, USP, is supplied in single-dose containers as follows:

List No.	Type Container	Concentration
3907	Glass Ampuls	20 mEq/10 mL
3934	Glass Ampuls	40 mEq/20 mL
4931	Glass Pintop Vials	10 mEq/5 mL
1498	Glass Pressurized Pintop Vials	30 mEq/15 mL
1499	Glass Pressurized Pintop Vials	40 mEq/20 mL
6635	Glass Fliptop Vials	10 mEq/5 mL
4932	Plastic Pintop Vials	20 mEq/10 mL
6651	Plastic Fliptop Vials	20 mEq/10 mL
6636	Plastic Fliptop Vials	30 mEq/15 mL
6653	Plastic Fliptop Vials	40 mEq/20 mL

Store at controlled room temperature 15° to 30°C (59° to 86°F) [See USP.]

Revised: April, 2004

HOSPIRA, INC., LAKE FOREST, IL 60045 USA

Hospira

POTASSIUM CHLORIDE
for Injection
Concentrate, USP

Rx only

CONCENTRATE

MUST BE DILUTED BEFORE USE.

FOR INTRAVENOUS INFUSION ONLY.
MUST BE DILUTED PRIOR TO INJECTION.

Ampuls
Fliptop Vials
Pintop Vials
Pressurized Pintop Vials

EN- 0069

DESCRIPTION

Potassium Chloride for Injection Concentrate, USP, is a sterile, nonpyrogenic, concentrated solution of potassium chloride, USP in water for injection administered by intravenous infusion only after dilution in a larger volume of fluid. They are provided in the following variety of concentrations and sizes comprising a choice of single-dose containers, all designed to provide the commonly prescribed amounts of potassium chloride for single-dose infusion after dilution in suitable large volume parenterals.

Additive Solution* (conc. & size)	K^+ mEq/mL	KCl mg/mL	mOsmol/mL (calc.)
0 mEq/20 mL	1.5	112	3
0 mEq/5mL	2	149	4
0 mEq/10 mL	2	149	4
0 mEq/15 mL	2	149	4
0 mEq/20 mL	2	149	4

*May contain hydrochloric acid for pH adjustment.

The solutions contain no bacteriostat, antimicrobial agent or added buffer (except for pH adjustment) and each is intended only for single-dose infusion (after dilution). When smaller doses are required, discard the unused portion. The pH is 4.6 (4.0 to 8.0).

Potassium Chloride for Injection Concentrate, USP (appropriately diluted) is a parenteral fluid and electrolyte replenisher.

Potassium Chloride, USP is chemically designated KCl, a white granular powder freely soluble in water.

The semi-rigid material used for the plastic vials is fabricated from a

specially formulated polyolefin. It is a copolymer of ethylene and propylene. The safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers. The container requires no vapor barrier to maintain the proper drug concentration.

CLINICAL PHARMACOLOGY

Potassium is the chief cation of body cells (160 mEq/liter of intracellular water) and is concerned with the maintenance of body fluid composition and electrolyte balance. Potassium participates in carbohydrate utilization and protein synthesis, and is critical in the regulation of nerve conduction and muscle contraction, particularly in the heart. Chloride, the major extracellular anion, closely follows the metabolism of sodium, and changes in the acid-base balance of the body are reflected by changes in the chloride concentration.

Normally about 80 to 90% of the potassium intake is excreted in the urine, the remainder in the stools and, to a small extent, in perspiration. The kidney does not conserve potassium well so that during fasting, or in patients on a potassium-free diet, potassium loss from the body continues, resulting in potassium depletion. A deficiency of either potassium or chloride will lead to a deficit of the other.

INDICATIONS AND USAGE

Potassium Chloride for Injection Concentrate, USP is indicated in the treatment of potassium deficiency states when oral replacement is not feasible.

CONTRAINDICATIONS

Potassium Chloride for Injection Concentrate, USP is contraindicated in diseases where high potassium levels may be encountered, and in patients with hyperkalemia, renal failure and in conditions in which potassium

retention is present.

WARNINGS

To avoid potassium intoxication, do not infuse solutions rapidly. In patients with severe renal insufficiency, administration of potassium chloride may cause potassium intoxication and life threatening hyperkalemia.

The administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema.

The risk of dilutional states is inversely proportional to the electrolyte concentration. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentration.

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

General

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the

condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require the use of additional electrolyte supplements, or the use of electrolyte-free dextrose solutions to which individualized electrolyte supplements may be added.

Potassium therapy should be guided primarily by serial electrocardiograms, especially in patients receiving digitalis. Serum potassium levels are not necessarily indicative of tissue potassium levels. Solutions containing potassium should be used with caution in the presence of cardiac disease, particularly in the presence of renal disease, and in such instances, cardiac monitoring is recommended.

Solutions containing dextrose should be used with caution in patients with overt or known subclinical diabetes mellitus, or carbohydrate intolerance for any reason.

If the administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Pregnancy

Teratogenic Effects: Pregnancy category C. Animal reproduction studies have not been conducted with potassium chloride. It is also not known whether potassium chloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Potassium chloride should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation, hypervolemia, and hyperkalemia.

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