PRODUCT MONOGRAPH

PrNUROMAX®

(doxacurium chloride)

1 mg/mL Injection

Intravenous Nondepolarizing Skeletal Neuromuscular Blocking Agent

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PRODUCT MONOGRAPH

NAME OF DRUG

PrNUROMAX®

(doxacurium chloride) Injection

THERAPEUTIC CLASSIFICATION

Intravenous Nondepolarizing Skeletal Neuromuscular Blocking Agent

CLINICAL PHARMACOLOGY

NUROMAX (doxacurium chloride) is a long-acting, nondepolarizing, skeletal neuromuscular blocking agent for intravenous administration. Nondepolarizing agents antagonize the neurotransmitter action of acetylcholine by binding competitively with cholinergic receptor sites on the motor end-plates. This antagonism is inhibited, and neuromuscular block reversed, by acetylcholinesterase inhibitors such as neostigmine.

Pharmacodynamics

Doxacurium chloride is approximately 2.5 to 3 times more potent than pancuronium and 10 to 12 times more potent than metocurine. Doxacurium chloride in doses of 1.5 to 2 x ED_{95} has a clinical duration of action (range and variability) similar to that of equipotent doses of pancuronium and metocurine (historic data and limited comparison).

The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of doxacurium chloride is 0.025 mg/kg (range: 0.020 to 0.033 mg/kg) in adults receiving balanced anesthesia.

An initial doxacurium chloride dose of 0.025 mg/kg (ED_{95}) administered after 10% to 100% recovery from an intubating dose of 1 mg/kg succinylcholine is followed by maximum block in about 9 to 10 minutes (range: 5 to 16 minutes). The duration of clinically effective neuromuscular block (i.e., time from injection to 25% recovery) is approximately 55 minutes (range: 9 to 145 minutes) during balanced anesthesia. (See Table 3 under **DOSAGE AND ADMINISTRATION**).

An initial dose of 0.05 mg/kg (2 x ED_{95}) in patients receiving balanced anesthesia, generally produces sufficient block for intubation within 4 to 5 minutes. Neuromuscular block reaches a maximum in 5 to 6 minutes (range: 2.5 to 13 minutes), and has a clinically effective duration of approximately 100 minutes (range: 39 to 232 minutes). (see Table 3 under **DOSAGE AND ADMINISTRATION**).

Intubation is generally possible 3 to 4 minutes after administration of a 0.08 mg/kg (3 x ED_{95}) dose. The time to onset of the maximum neuromuscular blocking effect averages 3.5 minutes (range: 2.4 to 5 minutes). Clinically effective block lasts for approximately 160 minutes (range 110 to 338 minutes). (see Table 3 under **DOSAGE AND ADMINISTRATION**).

As with other long-acting agents, the duration of neuromuscular block associated with doxacurium chloride shows considerable interpatient variability. An analysis of 390 cases in U.S. clinical trials utilizing a variety of premedications, varying lengths of surgery, and various anesthetic agents, indicates that approximately two-thirds of the patients had clinical durations within 30 minutes of the duration predicted by dose (based on mg/kg actual body weight). Patients ≥60 years old were approximately twice as likely to experience prolonged clinical duration (30 minutes longer than predicted) as patients <60 years old; thus, care should be used in these patients when prolonged recovery is undesirable (see **Geriatric Use** subsection of **PRECAUTIONS** and **Individualization of Dosages** subsection of **DOSAGE AND ADMINISTRATION**). In addition, obese patients (patients weighing ≥30% more than ideal body weight for height) were almost twice as likely to experience prolonged clinical duration as non-obese patients. Dosing for obese patients should therefore be based on ideal body weight (see **Individualization of Dosages** subsection of **DOSAGE AND ADMINISTRATION**).

Most patients receiving doxacurium chloride in clinical trials required pharmacologic reversal prior to full spontaneous recovery from neuromuscular block; therefore, relatively few data are available on the time from injection to 95% recovery of the twitch response. As a class, long-acting neuromuscular blocking agents may be associated with prolonged times to full spontaneous recovery. Some patients may require as long as 3 to 4 hours to exhibit full spontaneous recovery following initial doses of 0.025 to 0.05 mg/kg doxacurium chloride and even longer following an initial dose of 0.08 mg/kg.

Cumulative neuromuscular blocking effects are not associated with the repeated administration of maintenance doses of doxacurium chloride at 25% twitch recovery. Therefore, in a particular patient, maintenance doses can be administered at relatively regular intervals with predictable results. As with initial doses, however, the duration of action following maintenance doses of doxacurium chloride may vary considerably between patients.

To achieve comparable levels of block, children require higher doxacurium chloride doses on a mg/kg basis than do adults. The doxacurium chloride ED_{95} for children 2 to 12 years of age receiving halothane anesthesia is approximately 0.03 mg/kg. The onset time and duration of block are shorter in children than in adults. During halothane anesthesia, doses of 0.03 mg/kg and 0.05 mg/kg doxacurium chloride produce maximal block in approximately 7 and 4 minutes, respectively. The duration of clinically effective block is approximately 30 minutes after an initial dose of 0.03 mg/kg and approximately 45 minutes after 0.05 mg/kg. Doxacurium chloride has not been studied in children under 2 years of age.

The neuromuscular block produced by doxacurium chloride may be antagonized by anticholinesterase agents. As with other nondepolarizing neuromuscular blocking agents, the deeper the level of neuromuscular block at reversal, the longer is the time required for recovery of neuromuscular function.

Hemodynamics

Administration of doxacurium chloride doses up to and including 0.08 mg/kg (approximately 3 x ED_{95}) over 5 to 15 seconds revealed no dose-related effects on mean arterial blood pressure (MAP) or heart rate (HR) in healthy adult patients during steady state balanced anesthesia or in patients with serious cardiovascular disease undergoing coronary artery bypass grafting, cardiac valvular repair or vascular repair. In 2 to 12 year old children receiving halothane anesthesia, no dose related changes in MAP or HR were observed following the administration of up to 0.05 mg/kg doxacurium chloride over 5 to 15 seconds.

Doxacurium chloride doses of 0.03 to 0.08 mg/kg (1.2 to 3 x ED_{95}) were not associated with dose-dependent changes in mean plasma histamine concentration. Clinical experience with more than 1000 patients indicates that adverse reactions typically associated with histamine release (e.g., bronchospasm, hypotension, tachycardia, cutaneous flushing, urticaria, etc.) are infrequent following the administration of doxacurium chloride (see **ADVERSE REACTIONS**).

Pharmacokinetics

Pharmacokinetic and pharmacodynamic results from a study of 24 healthy young patients and 8 healthy elderly patients are summarized in Table 1. The pharmacokinetics are linear over the dosage range tested (i.e., plasma concentrations are approximately proportional to dose). The pharmacokinetics of doxacurium chloride are similar in healthy young adult and elderly patients. Some healthy elderly patients tend to be more sensitive to the neuromuscular blocking effects than healthy young adult patients receiving the same dose. The time to maximum block is longer in elderly patients than in young adult patients (11.2 minutes vs 7.7 minutes at 0.025 mg/kg doxacurium chloride). In addition, the clinically effective durations of block are more variable and tend to be longer in some healthy elderly patients than in healthy young adult patients receiving the same dose.

Table 1
Pharmacokinetic and Pharmacodynamic Parameters[1] of NUROMAX in Young Adult and Elderly Patients (Isoflurane Anesthesia)

Parameter	Healthy Young Adult Patients (22 to 49 years)			Healthy Elderly Patients (67 to 72 years)
	0.025 mg/kg (n = 8)	0.05 mg/kg (n = 8)	0.08 mg/kg (n = 8)	0.025 mg/kg (n = 8)
t½ elimination (min)	86 (25-171)	123 (51-163)	98 (47-163)	96 (50-114)
Volume of distribution at steady state (L/kg)	0.15 (0.10-0.21)	0.24 (0.13-0.30)	0.22 (0.16-0.33)	0.22 (0.14-0.40)
Plasma clearance (mL/min/kg)	2.22 (1.02-3.95)	2.62 (1.21-5.70)	2.53 (1.88-3.38)	2.47 (1.58-3.60)
Maximum block (%)	97 (88-100)	100 (100-100)	100 (100-100)	96 (90-100)
Clinical Effective Duration of block[2] (min)	68 (35-90)	91 (47-132)	177 (74-268)	97 (36-179)

[1] Values shown are mean (range).
[2] Time from injection to 25% recovery of the control twitch height

Table 2 summarizes the pharmacokinetic and pharmacodynamic results from a study of 9 healthy young patients, 8 patients with end-stage kidney disease undergoing kidney transplantation, and 7 patients with end-stage liver disease undergoing liver transplantation. The results suggest that a longer $t_{½}$ can be expected in patients with end-stage kidney disease; in addition, these patients may be more sensitive to the neuromuscular blocking effects of doxacurium chloride. The time to maximum block was slightly longer and the clinically effective duration of block was prolonged in patients with end-stage kidney disease.

Table 2
Pharmacokinetic and Pharmacodynamic Parameters[1] of NUROMAX in Healthy Patients and in Patients with End-Stage Kidney or Liver Disease (Isoflurane Anesthesia)

Parameter	Healthy Young Adult Patients	Kidney Transplant Patients	Liver Transplant Patients
	0.015 mg/kg (n = 9)	0.015 mg/kg (n = 8)	0.015 mg/kg (n = 7)
$t_{½}$ elimination (min)	99 (48-193)	221 (84-592)	115 (69-148)
Volume of distribution at steady state (L/kg)	0.22 (0.11-0.43)	0.27 (0.17-0.55)	0.29 (0.17-0.35)
Plasma clearance (mL/min/kg)	2.66 (1.35-6.66)	1.23 (0.48-2.40)	2.30 (1.96-3.05)
Maximum block (%)	86 (59-100)	98 (95-100)	70 (0-100)
Clinical effective duration of block[2] (min)	36 (19-80)	80 (29-133)	52 (20-91)

[1] Values shown are mean (range).
[2] Time from injection to 25% recovery of the control twitch height

The pharmacokinetics of doxacurium chloride are not significantly altered in liver transplant patients. Sensitivity to the neuromuscular blocking effects of doxacurium chloride was highly variable in patients undergoing liver transplantation. Three of 7 patients developed ≤50% block, suggesting that these patients may have a reduced sensitivity to this drug. In those patients who developed >50% neuromuscular block, the time to maximum block and the clinically effective duration of action tended to be longer than in healthy young adult patients (see **Individualization of Dosages** subsection of **DOSAGE AND ADMINISTRATION**). No data are available from patients with liver disease not requiring transplantation.

Consecutively administered maintenance doses of 0.005 mg/kg doxacurium chloride, each given at a 25% T_1 recovery following the preceding dose, do not result in a progressive increase in the plasma concentration of doxacurium or a progressive increase in the depth or duration of block produced by each dose.

Doxacurium chloride is not metabolized *in vitro* in fresh human plasma. Plasma protein binding of doxacurium chloride is approximately 30% in human plasma.

In vivo data from humans suggest that doxacurium chloride is not metabolized and that the major elimination pathway is excretion of the unchanged drug in urine and bile. In studies of healthy adult

patients, 24% to 38% of an administered dose was recovered as parent drug in the urine over 6 to 12 hours after dosing. High bile concentrations of doxacurium chloride (relative to plasma) have been found 35 to 90 minutes after administration in patients undergoing cholecystectomy. The overall extent of biliary excretion is unknown. The data derived from analysis of human urine and bile are consistent with data from *in vitro* studies in the rat, cat and dog, which indicate that all of an administered dose of doxacurium chloride is recovered as parent drug in the urine and bile of these species.

INDICATIONS AND CLINICAL USE

NUROMAX (doxacurium chloride) is a long-acting neuromuscular blocking agent, indicated as an adjunct to general anesthesia to provide skeletal muscle relaxation during surgery or mechanical ventilation. Doxacurium chloride may also be used for non-emergency tracheal intubation.

CONTRAINDICATIONS

NUROMAX (doxacurium chloride) is contraindicated in patients who have a known hypersensitivity to doxacurium chloride.

In newborn infants (children less that 1 month of age), benzyl alcohol has been associated with an increased incidence of neurological and other complications which are, sometimes fatal. Products from multiple-dose vials containing benzyl alcohol should not be used in newborn infants. DOXACURIUM HAS NOT BEEN STUDIED IN CHILDREN LESS THAN 2 YEARS OLD.

WARNINGS

NUROMAX (DOXACURIUM CHLORIDE) SHOULD BE USED ONLY BY THOSE TRAINED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR TRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS DOXACURIUM CHLORIDE SHOULD EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTICHOLINESTERASE ANTAGONISM.

Doxacurium chloride has no known effect on consciousness, pain threshold, or cerebration. To avoid distress to the patient, neuromuscular block should not be induced before unconsciousness.

Doxacurium chloride Injection is acidic (pH 4.0 to 5) and should not be mixed with alkaline solutions of pH >8.5 (e.g., barbiturate solutions).

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (e.g., myasthenia gravis, myasthenic [Eaton-Lambert] syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (e.g., carcinomatosis), the use of a peripheral nerve stimulator and a small test dose of doxacurium chloride may be of value in assessing the level of neuromuscular block and monitoring dosage requirements. Muscle relaxants with a shorter duration of action than NUROMAX may be more suitable for these patients.

PRECAUTIONS

General

NUROMAX (doxacurium chloride) has no clinically significant effects on heart rate; therefore doxacurium chloride will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

No data are available to support the use of doxacurium chloride by intramuscular injection.

Burns

Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns depending upon the time elapsed since the injury and the size of the burn. Doxacurium chloride has not been studied in patients with burns.

Electrolyte Abnormalities

Acid/base and/or serum electrolyte abnormalities may antagonize or potentiate the action of neuromuscular blocking agents. For example, hyperkalemia has been reported to antagonize nondepolarizing neuromuscular blockers, while hypokalemia has been associated with an enhancement of their activity.

Asthma

As doxacurium chloride has not been studied in patients with asthma or a history of severe anaphylactoid reactions, it should be administered with caution to these patient groups.

Renal and Hepatic Disease

The effects of renal and hepatic dysfunction on the action of doxacurium chloride have been studied in patients with end-stage kidney (n=8) or liver (n=7) disease undergoing kidney and liver transplantation (see **CLINICAL PHARMACOLOGY**). The possibility of prolonged neuromuscular block in patients undergoing renal transplantation, and the possibility of a variable onset and duration of action in patients undergoing liver transplantation, must be considered when doxacurium chloride is used in such patients.

Obesity

In obese patients, administration of doxacurium chloride on the basis of actual body weight is associated with prolonged neuromuscular blockade. Ideal body weight should be considered in dosage calculations for obese patients, and appropriate attention paid to the attendant risk of underdosing. Severe obesity may pose airway or ventilatory problems requiring special care before, during, or after the use of nondepolarizing neuromuscular blockers such as doxacurium chloride.

Malignant Hyperthermia (MH)

Doxacurium chloride has not been studied in MH-susceptible patients. In a study of MH-susceptible Pietrain pigs (n=8) doxacurium chloride did not trigger MH. Since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia.

Hypothermia

Hypothermia (25 to 28°C) has been associated with a decreased requirement for nondepolarizing neuromuscular blocking agents.

Long-Term Use in the Intensive Care Unit (ICU)

The long-term use of doxacurium chloride in patients undergoing mechanical ventilation in the intensive care unit has not been studied. When there is a need for long-term mechanical ventilation, the relative benefits and risks of inducing neuromuscular block with doxacurium chloride must be considered.

Drug Interactions

Doxacurium chloride has been administered following succinylcholine-facilitated tracheal intubation. Prior administration of succinylcholine has no clinically important effect on the neuromuscular blocking action of doxacurium chloride. The depth, onset, and duration of neuromuscular block produced by an ED_{95} dose of doxacurium chloride given in the absence of prior administration of succinylcholine was not consistently altered when the same dose was given after complete (95%) or partial (10%) recovery from an intubating dose of succinylcholine. The administration of doxacurium chloride before succinylcholine to attenuate succinylcholine-induced side effects (e.g., muscle fasciculations, postoperative myalgia) has not been studied.

There are no clinical data on the concomitant use of doxacurium chloride and other

nondepolarizing neuromuscular blocking agents.

Isoflurane, enflurane and halothane reduce the ED_{50} of doxacurium chloride by 30% to 45%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as doxacurium chloride include certain antibiotics (e.g., aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine.

Concomitant phenytoin and carbamazepine treatment may be associated with an increase in the onset time of doxacurium chloride and a decrease in its duration of block. Similar interactions have been reported for other nondepolarizing neuromuscular relaxants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and fertility studies have not been performed. Doxacurium chloride was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, in the mouse lymphoma assay, and in the human lymphocyte assay. In the *in vivo* rat bone marrow cytogenetic assay, statistically significant increases in the incidence of structural abnormalities, relative to vehicle controls, were observed in male rats dosed with 0.1 mg/kg (0.625 mg/m^2) doxacurium chloride and sacrificed at 6 hours, but not at 24 or 48 hours, and in female rats dosed with 0.2 mg/kg (1.25 mg/m^2) doxacurium chloride and sacrificed at 24 hours, but not at 6 or 48 hours. There was no increase in structural abnormalities in either male or female rats given 0.3 mg/kg (1.875 mg/m^2) doxacurium chloride and sacrificed at 6, 24, or 48 hours. Thus, the incidence of abnormalities in the *in vivo* rat bone marrow cytogenetic assay was not dose-dependent and, therefore, the likelihood that the observed abnormalities were treatment-related or clinically significant is low.

Use in Pregnancy

Doxacurium chloride was not shown to be teratogenic when given to nonventilated pregnant rats and mice by the subcutaneous route at sub-paralyzing doses. Studies at paralyzing doses have not been performed. There are no studies in pregnant women. Because animal reproduction studies have not been performed under conditions that would approximate those of clinical use, doxacurium chloride should not be used during pregnancy unless, in the opinion of the physician, the potential benefits outweigh the unknown hazards. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

Labor and Delivery

As the duration of action of doxacurium chloride exceeds that of operative obstetrics, this drug is not recommended for use in patients undergoing caesarean section. The use of doxacurium chloride during labor or during vaginal delivery or caesarean section has not been studied. It is not known whether doxacurium chloride administered to the mother has immediate or delayed effects on the fetus.

Nursing Mothers

It is not known whether doxacurium chloride is excreted in human milk. Because many drugs are

excreted in human milk, caution should be exercised when doxacurium chloride is administered to a nursing woman.

Use in Children

For children 2 to 12 years of age, see Clinical Pharmacology and Dosage and Administration. The safety and efficacy of doxacurium chloride in children less than 2 years of age have not been studied.

Geriatric Use

Doxacurium chloride has been used in elderly patients, including patients with significant cardiovascular disease. In elderly patients, the onset of maximum block is slower and the duration of neuromuscular block produced by doxacurium chloride is more variable, and in some cases longer, than in young adult patients. (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). As with other long-acting neuromuscular blocking agents, the possibility of prolonged block must be considered when doxacurium chloride is administered to elderly patients, especially those known to have reduced liver or kidney function.

Increased Volume of Distribution

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

ADVERSE REACTIONS

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the pharmacological action beyond the time needed for surgery and anesthesia. This effect may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea which require manual or mechanical ventilation until recovery is judged to be clinically adequate (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE**). Inadequate reversal of neuromuscular block is possible with NUROMAX (doxacurium chloride), as with all nondepolarizing agents. Prolonged neuromuscular block and inadequate reversal may lead to postoperative complications.

Observed in Clinical Trials

Adverse experiences were uncommon among the 1034 surgical patients and volunteers who received doxacurium chloride and other drugs in U.S. clinical studies in the course of a wide variety of procedures conducted during balanced or inhalational anesthesia. The following adverse experiences were reported in patients administered doxacurium chloride (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence greater than 1%: none

Incidence less than 1% -

Cardiovascular:*	hypotension,† flushing,† ventricular fibrillation, myocardial infarction
Respiratory:	bronchospasm, wheezing
Dermatological:	urticaria, injection site reaction
Special Senses:	diplopia
Nonspecific:	difficult neuromuscular block reversal, prolonged drug effect, fever

* Reports of ventricular fibrillation (n=1) and myocaridal infarction (n=1) were limited to ASA class 3 to 4 patients undergoing cardiac surgery (n=142)

† 0.3% incidence. All other reactions unmarked were ≤0.1%.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The possibility of iatrogenic overdose can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Because a long duration of neuromuscular block may result from overdose, a peripheral nerve stimulator should be used to monitor recovery. Residual neuromuscular block beyond the time needed for surgery and anesthesia may occur with NUROMAX (doxacurium chloride) as with other neuromuscular blocking agents. This may be manifested by skeletal muscle weakness, low tidal volume, or apnea. A nerve stimulator may be used to differentiate residual neuromuscular block from other causes of apnea or decreased tidal volume, such as narcotics, barbiturates, or other central nervous system depressants. The primary treatment of overdose with nondepolarizing neuromuscular blocking agents is maintenance of a patent airway and manual or mechanical ventilation until recovery of normal respiration is assured. Recovery may be facilitated by administration of an anticholinesterase agent such as neostigmine in conjunction with an appropriate anticholinergic agent. In general, as with other nondepolarizing neuromuscular blocking agents, reversal should not be attempted until evidence of spontaneous recovery from neuromuscular block is present (see **Reversal** under **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION

NURAMAX (doxacurium chloride) SHOULD BE ADMINISTERED ONLY INTRAVENOUSLY.

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

Like other long-acting neuromuscular blocking agents, doxacurium chloride displays variability in the duration of its effect, and has the potential for prolonged clinical duration. The dosage information provided below is intended as a guide only. Doses should be individualized (see **Individualization of Dosage**). Factors that may warrant dosage adjustment include: advanced age, concomitant drug treatment, type of surgical procedure or general anesthetic, the presence of kidney or liver disease, or obesity (patients weighing $\geq$30% more than ideal body weight for height). The use of peripheral nerve stimulator will permit the most advantageous use of doxacurium chloride and minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Adults

The recommended dosage range of doxacurium chloride in adults receiving balanced anesthesia is 0.025 to 0.08 mg/kg (1 to 3 times the ED_{95} value). The potency of doxacurium chloride is enhanced by halogenated anesthetics. If doxacurium chloride is administered during steady-state isoflurane, enflurane, or halothane anesthesia, initial and maintenance doses should be reduced by approximately one-third.

In North American clinical trials performed in ASA 1 and 2 adults, the following ED_{95} values were obtained for doxacurium chloride in the presence of different anesthetic agents:

Anesthetic	NUROMAX ED_{95} (mg/kg)
Thiopental-Narcotic	0.02-0.03
Enflurane	0.014-0.015
Isoflurane	0.015-0.016
Halothane	0.014-0.025

The following table and the information provided below are intended as a guide only. Doses should be individualized (see **Individualization of Dosages** subsection below).

Table 3
Pharmacodynamic Characteristics[1] of NUROMAX Administered at Recommended Initial Dosages to Adult Surgical Patients (ASA 1 and 2) in Clinical Trials (Balanced Anesthesia)

Dose	0.025 mg/kg (ED_{95}) n = 34	0.05 mg/kg (2 x ED_{95}) n = 27	0.08 mg/kg (3 x ED_{95}) n = 9
Time to intubation (min)	Pre-intubation with succinylcholine required[2]	35889	35857
Time to maximum twitch suppression (min)	9.3 (5.4-16)	5.2 (2.5-13)	3.5 (2.4-5)
Time to 25% recovery (i.e., effective clinical duration)[1] (min)	55 (9-145)	100 (39-232)	160 (110-338)

[1] Values shown are means followed by the range of individual values in parentheses.
[2] NUROMAX was administered after 10-100% recovery from an intubating dose of succinylcholine

Initial doses (See Table 3)

An initial 0.025 mg/kg (ED_{95}) dose of doxacurium chloride administered during balanced anesthesia should be preceded by pre-intubation with succinylcholine. Doxacurium chloride may be given as soon as recovery from the effects of succinylcholine becomes evident. An initial dose of 0.025 mg/kg doxacurium chloride provides approximately 60 minutes of clinically effective neuromuscular block for surgery.

When administered as a component of a thiopental/narcotic induction-intubation paradigm with the intention to produce a long duration of neuromuscular block during surgery, an initial 0.05 mg/kg (2 x ED_{95}) dose of doxacurium chloride generally produces good-to-excellent conditions for tracheal intubation in approximately 4 to 5 minutes. Clinically effective neuromuscular block following a dose of 0.05 mg/kg doxacurium chloride may be expected to last approximately 100 minutes in patients receiving balanced anesthesia.

An initial dose of 0.08 mg/kg (3 x ED_{95}) doxacurium chloride should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated. Good-to-excellent intubation conditions may generally be expected approximately 3 to 4 minutes after administration of this dose. Clinically effective block may be expected to persist for 160 minutes or more.

Maintenance Doses

The need for maintenance dosing should be based on use of a peripheral nerve stimulator and/or clinical criteria. Maintenance doses will generally be required about 60 minutes after an initial dose of 0.025 mg/kg doxacurium chloride or 100 minutes after an initial dose of 0.05 mg/kg doxacurium chloride during balanced anesthesia. Repeated maintenance doses administered at 25% twitch recovery may be expected to be required at relatively regular intervals in individual patients. The interval may vary considerably between patients. Maintenance doses of 0.005 and 0.01 mg/kg doxacurium chloride provide an average 30 minutes (range: 9 to 57 minutes) and 45 minutes (range: 14 to 108 minutes) respectively, of additional clinically effective neuromuscular block. For shorter and longer desired durations, smaller or larger maintenance doses may be administered.

If doxacurium chloride is administered during steady-state isoflurane, enflurane, or halothane anesthesia, maintenance doses should be reduced by approximately 30 to 40%.

Children

Dose-response studies in children 2 to 12 years of age indicate that the dose requirements for doxacurium chloride on a mg/kg basis are higher in children than in adults and that recovery from neuromuscular block induced by doxacurium chloride occurs more rapidly. In children anesthetized with halothane, an initial doxacurium chloride dose of 0.03 mg/kg (ED_{95}) produces maximal block in about 7 minutes (range: 5 to 11 minutes), and clinically effective block persists for approximately 30 minutes (range: 12 to 54 minutes). An initial dose of 0.05 mg/kg produces maximal block in about 4 minutes (range: 2 to 10 minutes), and clinically effective block persists for approximately 45 minutes (range: 30 to 80 minutes). Maintenance doses of doxacurium chloride may be required with slightly greater frequency in children than in adults. Because of the potentiating effect of halothane, a higher dose of doxacurium chloride may be required in children receiving balanced anesthesia than in children receiving halothane anesthesia to achieve a comparable onset and duration of neuromuscular block. Doxacurium chloride has not been studied in children under two years of age.

Reversal

Once spontaneous recovery is evident, reversal of the neuromuscular block produced by doxacurium chloride can be achieved with various anticholinesterase agents such as neostigmine in conjunction with an appropriate anticholinergic agent. As with other nondepolarizing neuromuscular blocking agents, the time required for anticholinesterase-mediated recovery may be lengthened if reversal is attempted at a deep level of block or if inadequate doses of reversal agent are employed.

In clinical trials, a dose of 1 mg/kg edrophonium was not as effective as a dose of 0.06 mg/kg neostigmine in antagonizing moderate to deep levels of neuromuscular block (i.e., <60% T_1 recovery). Therefore, the use of 1 mg/kg edrophonium is not recommended for reversal of moderate to deep levels of block. The use of pyridostigmine has not been studied.

Patients should be evaluated for adequate clinical evidence of antagonism, e.g., 5-second head lift, and grip strength. Ventilation must be supported until no longer required. As with other neuromuscular blocking agents, physicians should be alert to the possibility that the action of the drugs used to antagonize neuromuscular block may wear off before the effects of doxacurium chloride on the neuromuscular junction have declined sufficiently.

Antagonism may be delayed in the presence of debilitation or carcinomatosis, and during the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or cause respiratory depression (see **Drug Interactions** subsection of **PRECAUTIONS**). Under such circumstances the management is the same as that of prolonged neuromuscular block.

Individualization of Dosages

Recommended doses of doxacurium chloride are more likely to be associated with a prolonged duration of clinically effective block in the elderly or in patients with obesity or renal impairment than in healthy young adult patients of normal body weight (see **CLINICAL PHARMACOLOGY**). In elderly patients or patients who have kidney disease, the potential for a prolongation of block may be reduced by decreasing the initial doxacurium chloride dose and by titrating the dose to achieve the desired depth of block. For obese patients (i.e., patients weighing ≥30% more than ideal body weight for height), ideal body weight should be used when determining the dose.

Dosage requirements for patients with serious liver disease are variable; some patients may require a higher than normal initial doxacurium chloride dose to achieve clinically effective block. Once adequate block is established, the clinical duration of block may be prolonged relative to patients with normal liver function.

At is the case with pancuronium, metocurine, and vecuronium, resistance to doxacurium chloride, manifested by a reduced intensity and/or shortened duration of block, must be considered when doxacurium chloride is selected for use in patients receiving phenytoin or carbamazepine (see **Drug Interactions** subsection of **PRECAUTIONS**). Similarly, a reduction in dosage of doxacurium chloride must be considered in cachectic or debilitated patients, in patients with neuromuscular diseases, severe electrolyte abnormalities, or carcinomatosis, and in other patients in whom potentiation of neuromuscular block or difficulty with reversal is anticipated. Increased doses of doxacurium chloride may be required in burn patients (see **PRECAUTIONS**).

PHARMACEUTICAL INFORMATION

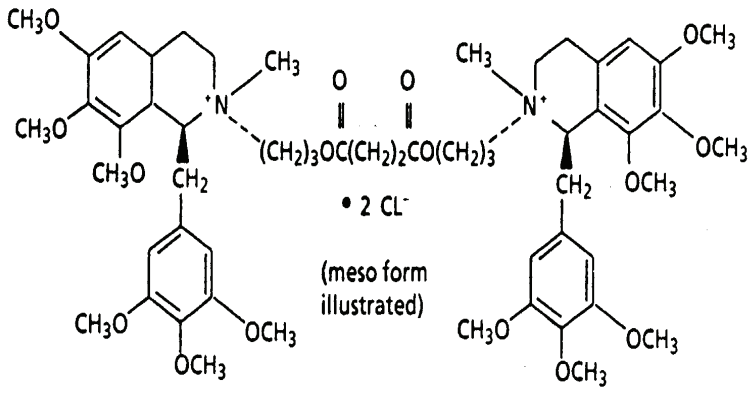
Drug Substance

Trade Name: NUROMAX

Proper Name: doxacurium chloride

Chemical Name: isoquinolinium,2,2' - [1,4 - dioxo - 1,4 - butanediyl) bis (oxy - 3,1 - propanediyl)] bis [1,2,3,4 - tetrahydro - 6,7,8 - trimethoxy - 2 - methyl - 1 - [(3,4,5 - trimethoxyphenyl) - methyl] -, dichloride

Structural Formula:



Molecular Formula: $C_{56}H_{78}Cl_2N_2O_{16}$

Molecular Weight: 1106.14

Description:

Doxacurium chloride is a mixture of three stereoisomers [(1*R*, 1′*S*, 2*S*, 2′*R*), a *meso* compound; and two enantiomers (1*R*, 1′*R*, 2*S*, 2′*S*) and (1*S*, 1′*S*, 2*R*, 2′*R*), respectively]. All stereoisomers have *trans* configurations between the groups in the 1- and 2- positions of the isoquinolinium rings as depicted in the molecular structure.

Doxacurium chloride is a white to off-white amorphous solid. It decomposes at approximately 160°C. Solubility at ambient temperature in distilled water: >100 mg/mL. Very soluble in ethanol, 0.1 N HCl, 0.1 N NaOH, 0.9% saline injection and 5% dextrose injection; freely soluble in 1-Octanol. The pH of a solution containing 1 mg/mL doxacurium chloride is between 4.0 and 6.0.

Composition

NUROMAX Injection vials contain 1.0 mg/mL doxacurium as doxacurium chloride, 0.9% benzyl alcohol as a preservative and may contain hydrochloric acid as a pH adjuster. The product has a final pH between 4.0 and 5.0.

Stability and Storage Recommendations

NUROMAX Injection should be stored at room temperature between 15° and 25°C. DO NOT FREEZE.

Parenteral Products

NUROMAX Injection may not be compatible with alkaline solutions with a pH greater than 8.5 (e.g., barbiturate solutions).

When administered through a y-site during intravenous infusion, doxacurium chloride is physically and chemically compatible with the following diluents:

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

NUROMAX diluted up to 1:10 in 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection, USP is physically and chemically stable stored in polypropylene syringes at room temperature, 15° to 25°C for up to 24 hours. Since dilution diminishes the preservative effectiveness of benzyl alcohol, aseptic techniques should be used to prepare the diluted product. Immediate use of the diluted product is preferred; any unused portion of diluted NUROMAX should be discarded after 8 hours.

AVAILABILITY OF DOSAGE FORMS

NUROMAX (doxacurium chloride) Injection, 1 mg doxacurium in each mL. 5 mL multiple-dose vials containing 0.9% w/v benzyl alcohol as a preservative. Store at room temperature between 15° and 25°C. NUROMAX DOES NOT REQUIRE REFRIGERATION. DO NOT FREEZE.

PHARMACOLOGY

The neuromuscular blocking properties of doxacurium have been demonstrated in cats (ED_{95} = 0.012 mg/kg i.v.), dogs (ED_{95} = 0.006-0.007 mg/kg i.v.), and monkeys (ED_{95} = 0.017 mg/kg i.v.). In cats and monkeys, doxacurium has a duration of action which is 2 to 3 times that of d-tubocurarine and 2 to 5 times that of atracurium. Blockade is of the nondepolarizing type exemplified by partial tetanic fade, post-tetanic potentiation, and antagonism by acetylcholinesterase inhibitors. In studies in which animals received repeated doses of doxacurium, cumulative effects were not apparent.

The effects of doxacurium on the autonomic nervous system have been examined in anesthetized cats in which the nictitating membrane response to preganglionic stimulation and the vasodepressor response to vagus nerve stimulation were recorded. Doxacurium produced no effects on the autonomic nervous system at doses up to 32 times the ED_{100}.

At doses which were 10 to 20 times the ED_{95}, doxacurium had minimal cardiovascular effects in anesthetized dogs or monkeys. Anesthetized dogs with a high degree of vagal tone did not exhibit any significant cardiovascular effects following the administration of doxacurium at doses of 5 to 10 times the $ED_{95\text{-}100}$.

Intravenous bolus doses up to 32 times the ED_{100} in anesthetized cats produced variable and transient effects on MAP and HR. In cats, dogs, and monkeys, the predominant effect of high overdoses was hypotension, a dose-dependent effect with a shorter duration than the neuromuscular paralysis.

No changes in the pharmacodynamics of doxacurium were noted between control sham-operated cats and cats with bilateral renal artery ligation suggesting that pathways other than renal clearance may contribute to the dissipation of neuromuscular blockade.

Pharmacokinetics

Various pharmacokinetic parameters were studied in the dog, cat, and Rhesus monkey. The following results were obtained:

Parameter	Dog	Cat	Rhesus Monkey
Dose	0.009 mg/kg i.v. (ED_{100})	0.020 mg/kg i.v. (ED_{100})	0.103 mg/kg (series of i.v. inj.) (ED_{95})
Clearance (Cl) (L/hr/kg)	0.18	0.22	0.47
Volume of Distribution at Steady State (Vdss) (L/kg)	0.12	0.12	0.34
Half-Life $t½_{\alpha}$ (min) $t½_{\beta}$ (min)	 2.1 25.7	 3.2 35.0	 3.0 38.3
AUC ($ng \cdot mL^{-1} \cdot min$)	2 369	6 691	16 634

In the cat and dog, approximately three-fourths of the administered dose is recovered in urine and one-fourth in bile. In the rat, approximately one-third of the dose is recovered in urine and two-thirds in bile.

TOXICOLOGY

Acute

The LD_{50} values of intravenous and subcutaneous injections of NUROMAX (doxacurium chloride) determined in the rat were 0.131 and 1.8 mg/kg, respectively.

Subacute

Doxacurium chloride was subcutaneously administered to non-ventilated rats at doses of 0.15 and 0.30 mg/kg/day for up to 14 consecutive days.

The dose of 0.30 mg/kg/day was considered to be the maximum tolerated dose in non-ventilated rats when dosed by the subcutaneous route. One male high-dose rat died on day seven exhibiting signs of neuromuscular blockade. No drug-related differences compared to control animals were found in evaluations of body weights, food consumption, hematology, and clinical chemistry, toxicologic and pharmacologic signs, and ophthalmologic evaluations.

Doxacurium chloride was administered to anesthetized, ventilated dogs and monkeys twice weekly for three weeks under conditions simulating clinical usage. The doses employed represented up to 9 x ED_{100} in dogs and 4.5 x ED_{95} in monkeys. Observations and measurements in these studies included appetite, clinical signs, body weight, ophthalmology, electrocardiography, clinical pathology, organ weights, gross pathology and histopathology. There were no definitive drug-related effects noted in either study.

In a second monkey study, the animals were dosed as above, but were administered either label strength doxacurium chloride or drug that had been heat degraded to 80% of label strength. There were no changes that could be attributed to either form of doxacurium chloride compared to control animals.

A study was conducted in dogs to evaluate the toxic effects of intravenously administered doxacurium chloride alone and in combination with its products of hydrolysis. Animals were dosed weekly for three weeks at doxacurium doses of 30 x ED_{100}. Some dogs experienced intermittent salivation during anesthesia. Minor decreases in red cell mass and elevations in leukocyte counts were noted. No other findings in the study could be attributed to drug administration.

Mutagenicity

Doxacurium chloride was not found to be mutagenic in the Ames Salmonella assay nor in the L5178Y/$TK^{+/-}$ mouse lymphoma assay. No structural or numerical chromosome observations were noted in cultured human lymphocytes exposed to doxacurium chloride in the presence or absence of metabolic activation.

An *in vivo* cytogenicity study in rats showed an increase in the incidence of structural chromosome damage in one male group and one female group of animals at the low and intermediate dose level respectively. The weak response was not dose-related and it is unlikely that it is related to treatment or of biological significance.

Teratology

Teratology studies were conducted in pregnant mice and rats. Doxacurium was administered subcutaneously at 2 dose levels including the maximum tolerated dose which did not cause neuromuscular blockade. Doxacurium was given on days 6 through 15, during the period of organogenesis. Doxacurium was not maternally toxic, teratogenic, or embryotoxic. However, as doxacurium was administered by the subcutaneous route at sub-paralysing doses, the relevance of these studies to the clinical use of the drug cannot be assessed.

Special Studies

Doxacurium chloride was tested for its potential to excite malignant hyperthermia in susceptible Pietrain pigs. No evidence of malignant hyperthermia was seen at doses of 1 and 4 x ED_{95} of doxacurium chloride. The susceptibility of the pigs to the development of malignant hyperthermia was later confirmed by other agents both *in vivo* and in a muscle biopsy *in vitro* system.

Doxacurium chloride was shown to be nonirritating when injected perivenously or intramuscularly in dogs as a 0.5 mL solution of 1 mg/mL doxacurium.

A 1 mg/mL solution of doxacurium chloride did not flocculate plasma protein nor excessively hemolyze a 50% suspension of red blood cells when tested at 1:1 or 1:4 ratios with human type O positive plasma or red blood cell suspensions. The hemolysis seen was no different from that caused by sterile water for injection and was greater than that caused by isotonic saline.

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