Neuromuscular Blockade in the ICU

NIMBEX® (cisatracurium besylate) is indicated as an adjunct to general anesthesia to facilitate tracheal intubation in adults and in pediatric patients 1 month to 12 years of age; to provide skeletal muscle relaxation in adults during surgical procedures or mechanical ventilation in the ICU; and to provide skeletal muscle relaxation during surgical procedures via infusion in pediatric patients 2 years and older. NIMBEX is not recommended for rapid sequence endotracheal intubation.

Safety Considerations

NIMBEX is contraindicated in patients with known hypersensitivity to cisatracurium. Severe anaphylactic reactions to NIMBEX have been reported. Use of 10-mL NIMBEX multiple-dose vials is contraindicated for use in pediatric patients less than 1 month of age and low birth-weight infants because the formulation contains benzyl alcohol. NIMBEX has been associated with residual paralysis; patients with neuromuscular diseases and carcinomatosis may be at higher risk. Patients with renal or hepatic impairment receiving extended administration of NIMBEX may be at higher risk of seizures.

Please see Important Safety Information on page 6.
Please see accompanying full prescribing information.
Neuromuscular Blockers (NMBs) May Be Used in the ICU for:

Facilitating mechanical ventilation by stopping spontaneous breathing efforts and preventing patient-ventilator dyssynchrony

Safety Considerations:

- Severe hypersensitivity reactions to NiMBex have been reported, including life-threatening and fatal anaphylactic reactions. Precaution should be taken in those patients who have had previous anaphylactic reactions to other neuromuscular blocking agents.

- Administer NiMBex in carefully adjusted dosage by or under the supervision of experienced clinicians who are familiar with the drug’s actions and the possible complications.

- Adverse reactions occurred among the 68 ICU patients who received NiMBex in conjunction with other drugs in US and European clinical studies. One out of 68 patients experienced bronchospasm. In one study, there were 2 reports of prolonged recovery among 28 patients administered NiMBex compared with 13 reports among 30 patients administered vecuronium.

ICU patients may be mechanically ventilated for the following reasons:

- Acute respiratory distress syndrome (ARDS)
- Pneumonia
- Bacteremia/sepsis
- Head trauma
- Intracranial hemorrhage
- Blunt/penetrating chest or abdominal trauma
- Post-operative complications
- Therapeutic hypothermia

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Important Considerations When Caring for a Patient on a Neuromuscular Blocker

The ICU patient on a neuromuscular blocking agent is completely paralyzed (i.e., unable to breathe, cannot blink, no swallowing or gag reflex, etc.). They are dependent on the ICU team to protect them from potential complications. The following are recommendations to provide patient safety:

- Provide adequate sedation and analgesia (NMBs have no sedative or analgesic properties; always use with a sedative for amnesia to minimize patient recall)
- Use a twitch monitor to assess the patient’s train-of-four responses and document the level of paralysis
- Always deliver the lowest effective dose of the NMB; to ensure the dose is not excessive, allow some muscle stimulation to occur
- Protect the patient’s eyes with the use of artificial tears
- Position the patient so as to protect pressure points
- Address deep vein thrombosis
  - Sequential compression boots
  - Chemical anticoagulation
- Prevent stress ulcers
- Administer mouth washes
- Elevate the head of the bed to prevent ventilator-associated pneumonia
- Monitor pupillary reflexes to assess neurologic status
- Schedule a neuromuscular blocker “holiday” every 12-24 hours to assess need for continued use
Why Monitoring Is Important

Close monitoring of patients receiving NMBs is important for several reasons:

- To assess the depth and duration of neuromuscular blockade, which can vary from patient to patient
- To help determine when additional doses are needed
- To assess recovery from the block
- To prevent overdose

Monitoring With Train of Four

Monitoring a patient’s responses to a series of four peripheral-nerve stimuli (“train of four”) can help you assess the degree of neuromuscular blockade.

Please see Important Safety Information on page 6.
Please see accompanying full prescribing information.
How to Monitor With Train of Four

How It Works:

• A battery-powered stimulator delivers a small electric current to a superficial nerve, usually the ulnar nerve
• Activity stimulated by the four consecutive impulses is assessed by watching or feeling for associated muscle movement
• The muscle movement (“twitch”) observed is used to estimate the level of blockade (see the chart below)

Things to Keep in Mind:

• Adequate muscle relaxation exists when 2 of 4 twitches are present
• Good intubating conditions exist when 1 of 4 twitches remains
• It is important to take the patient off the NMB periodically to determine if it is still needed

Train-of-Four Responses

<table>
<thead>
<tr>
<th>Response</th>
<th>Approximate % of Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four twitches</td>
<td>0-75</td>
</tr>
<tr>
<td>Three twitches</td>
<td>75</td>
</tr>
<tr>
<td>Two twitches</td>
<td>80</td>
</tr>
<tr>
<td>One twitch</td>
<td>90</td>
</tr>
<tr>
<td>Twitches absent</td>
<td>100</td>
</tr>
</tbody>
</table>
NiMBex: Overview

Indication

NIMBEX® (cisatracurium besylate) is indicated as an adjunct to general anesthesia to facilitate tracheal intubation in adults and in pediatric patients 1 month to 12 years of age; to provide skeletal muscle relaxation in adults during surgical procedures or mechanical ventilation in the ICU; and to provide skeletal muscle relaxation during surgical procedures via infusion in pediatric patients 2 years and older. NIMBEX is not recommended for rapid sequence endotracheal intubation.

Safety Considerations

NIMBEX is contraindicated in patients with known hypersensitivity to cisatracurium. Severe anaphylactic reactions to NIMBEX have been reported. Use of 10-mL NIMBEX multiple-dose vials is contraindicated for use in pediatric patients less than 1 month of age and low birth-weight infants because the formulation contains benzyl alcohol. NIMBEX has been associated with residual paralysis; patients with neuromuscular diseases and carcinomatosis may be at higher risk. Patients with renal or hepatic impairment receiving extended administration of NIMBEX may be at higher risk of seizures.

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Please see accompanying full prescribing information.
NiMBex Pharmacokinetics

NiMBex Elimination

• NiMBex is cleared from the body primarily through organ-independent Hofmann elimination (a chemical process dependent on pH and temperature).

NiMBex Hemodynamic Profile

• NiMBex does not cause dose-related increases in histamine concentration.
  - A study by Lien et al. comparing equipotent doses of atracurium and NiMBex in healthy patients showed no histamine release (up to and including 8 x ED$_{95}$) when administered over 5 to 10 seconds.$^4$

• NiMBex does not cause dose-related effects on mean arterial blood pressure or heart rate.
  - In a study by Searle et al. comparing NiMBex and vecuronium, the rapid administration of NiMBex (at doses up to 4 x ED$_{95}$) administered over 5 to 10 seconds did not cause hemodynamic side effects in patients with CAD.$^5$

• Severe hypersensitivity reactions to NiMBex have been reported, including life-threatening and fatal anaphylactic reactions. Precaution should be taken in those patients who have had previous anaphylactic reactions to other neuromuscular blocking agents.
Neuromuscular Duration and Recovery:

A prospective, randomized, double-blind study compared the infusion requirements and recovery profiles of NiMBex and vecuronium in ICU patients.1,6

Findings:

- Average neuromuscular recovery time ($P=0.02$)
  - NiMBex: 68±13 minutes
  - Vecuronium: 387±163 minutes

- Reports of prolonged recovery ($P=0.002$)
  - NiMBex: 2 of 28 (7%)
  - Vecuronium: 13 of 30 (43%)

Safety Considerations1

The level of neuromuscular blockade during long-term NiMBex administration should be monitored with a nerve stimulator.

Please see Important Safety Information on page 6. Please see accompanying full prescribing information.
NiMBex Dosing Guidelines

In the ICU, NiMBex is indicated to facilitate mechanical ventilation.

Infusion Rates and Duration in the ICU:

- Average infusion rates of approximately 3 mcg/kg/min (range: 0.5 to 10.2) should provide adequate neuromuscular block in adults

Safety Considerations

The level of neuromuscular blockade during long-term NiMBex administration should be monitored with a nerve stimulator to titrate NiMBex administration to the patient’s needs and limit exposure to toxic metabolites.
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**Important Safety Information**

- NIMBEX is contraindicated in patients with known hypersensitivity to cisatracurium; severe anaphylactic reactions have been reported. The use of 10-mL NIMBEX multiple-dose vials is contraindicated in pediatric patients less than 1 month of age and low birth-weight infants because the formulation contains benzyl alcohol.
- NIMBEX has been associated with residual paralysis; patients with neuromuscular disease and carcinomatosis may be at higher risk. A lower maximum initial bolus is recommended in these patients to prevent complications.
- Serious and fatal adverse reactions including “gasping syndrome,” which is characterized by central nervous system depression, metabolic acidosis, and gasping respirations, can occur in neonates and infants treated with benzyl alcohol–preserved drugs, including NIMBEX 10-mL multiple-dose vials. Single-use vials (5-mL and 20-mL) of NIMBEX do not contain benzyl alcohol.
- Laudanosine, an active metabolite of NIMBEX, has been shown to cause seizures in animals. NIMBEX-treated patients with renal or hepatic impairment may have higher metabolite concentrations (including laudanosine) than patients with normal renal and hepatic function. Patients with renal or hepatic impairment receiving extended administration of NIMBEX may be at higher risk of seizures. The level of neuromuscular blockade during long-term NIMBEX administration should be monitored with a nerve stimulator to titrate NIMBEX administration to the patient’s needs and limit exposure to toxic metabolites.
- Severe hypersensitivity reactions to NIMBEX have been reported, including life-threatening and fatal anaphylactic reactions. There have been reports of wheezing, laryngospasm, bronchospasm, rash, and itching following NIMBEX administration in pediatric patients. Precaution should be taken in those individuals who have had previous anaphylactic reactions to other neuromuscular blocking agents.

Please see accompanying full prescribing information.
• Confirm proper selection of intended product, avoid confusion with other injectable solutions, and ensure that the intended dose is clearly labelled and communicated. Administration of NIMBEX results in paralysis, which may lead to respiratory arrest and death, a progression that may be more likely to occur in a patient for whom it is not intended.

• Neuromuscular blockade in the conscious patient can lead to distress. Use NIMBEX in the presence of appropriate sedation or general anesthesia. Monitor patients to ensure that the level of anesthesia is adequate.

• The 20-mL vial of NIMBEX is intended only for administration as an infusion for use in a single patient in the ICU. It should not be used multiple times because it does not contain a preservative, and there is a higher risk of infection.

• Certain drugs may enhance the neuromuscular blocking action of NIMBEX, including inhalational anesthetics, antibiotics, magnesium salts, lithium, local anesthetics, procainamide, and quinidine. Acid-base and/or serum electrolyte abnormalities may potentiate the action of neuromuscular blocking agents. Shorter durations of neuromuscular block may occur and NIMBEX infusion rate requirements may be higher in patients chronically administered phenytoin or carbamazepine. Use peripheral nerve stimulation and monitor clinical signs of neuromuscular blockade to determine adequacy of neuromuscular blockage and the need to adjust the NIMBEX dosage.

• NIMBEX has not been studied in patients susceptible to malignant hyperthermia (MH). Because MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient undergoing general anesthesia.

• The use of succinylcholine prior to NIMBEX may decrease the time to onset of maximum neuromuscular blockade but has no effect on the duration. Administration of inhalational anesthetics with nitrous oxide/oxygen for greater than 30 minutes to achieve 1.25 MAC may prolong the duration of action of initial and maintenance doses of NIMBEX. This may potentiate the neuromuscular blockade.

• Adverse reactions reported by <1% of the surgical patients treated with NIMBEX during clinical trials include bradycardia, hypotension, flushing, bronchospasm, and/or rash.

• Adverse reactions occurred among the 68 adult ICU patients who received NIMBEX in conjunction with other drugs in US and European clinical studies. One out of 68 patients experienced bronchospasm. In one study, there were 2 reports of prolonged recovery among 28 patients administered NIMBEX compared with 13 reports among 30 patients administered vecuronium.
References: