Drug shortage mitigation pearls

This document provides mitigation strategies for handling ongoing drug shortages to participants in the Vizient® Pharmacy Program. Information is compiled from mitigation strategies of institutions that serve on the Vizient Clinical Council and is reviewed by a panel of pharmacists.

For more information, contact pharmacyquestions@vizientinc.com.

Drug name or class: Neuromuscular blocking agents (NMBA)

Background
Please refer to ASHP's Drug Shortage website for the most up-to-date information. • Multiple manufacturers have reported a shortage of cisatracurium besylate injection due to increased demand. • Sun Pharma and AuroMedics have reported a shortage of vecuronium bromide injection. • Multiple manufacturers have reported a shortage of rocuronium bromide solution for injection due to increased demand.

Type(s) of mitigation strategies	
Check all that apply:	
☒ Therapeutic alternative/interchange	☒ Restriction criteria
☐ Compounding (insourcing)	☒ Change in dosage or administration schedule
☐ Compounding (outsourcing)	☐ Other; specify: _____

Detailed information
General conservation strategies • For NMBAs that are refrigerated, consider extended room temperature dating (if stability information available). • In consultation with infection control, extend hang time of IV solutions (eg, 96 hours or maximum stability). • Investigate max concentrations for infusions to reduce potential waste. • To reduce waste, develop a process to confirm need for refill bags for continuous infusions. **Intubation** *Note: Use of NMBAs improves first attempt success at intubation and reduces complications such as vomiting, muscle rigidity and laryngospasm, and apnea. The suggestions below may not represent best*

Detailed information

practices, but options to consider if there are shortages.[1-4] *If intubation is attempted without use of a NMBA, a rapid-acting NMBA should be on-hand.*[2]

- Prioritize use of succinylcholine over rocuronium or vecuronium for an induction agent in rapid sequence intubation (RSI), unless contraindications exist.
    - Use succinylcholine with extreme caution in patients with pre-existing hyperkalemia.
    - Eliminate use of defasciculation dose of nondepolarizing NMBA if used with succinylcholine.
- Consider ketamine-facilitated intubation (KFI) to avoid NMBA use.[2,5]
    - Awake approach: primary intervention is use of topical anesthesia (ie, topical and atomized lidocaine); ketamine may or may not be used to dissociate the patient along the way (ketamine is on-hand).
    - Ketamine-driven approach: primary intervention is use of ketamine at dissociative doses; topical anesthesia may or may not be used.
- May consider remifentanil intubation to avoid NMBA use.
    - Remifentanil is given at a bolus dose of 3 to 5 mcg/kg IV, in combination with propofol at a bolus dose of 2 to 2.5 mg/kg IV.[6]
    - Consider premedication with oral benzodiazepine (may prevent muscle rigidity) and concomitant administration of ephedrine 10 mg IV (may help prevent bradycardia and hypotension).[6]
    - Studies have suggested that remifentanil and propofol provide acceptable intubating conditions in 95% of patients.[7,8]
- May consider "awake" intubation to avoid NMBA use, which consist of regional anesthesia ("topicalization") and sedation for intubation
    - For topicalization, use of both viscous and nebulized lidocaine (4%) can be employed:[9,10]
        - Viscous lidocaine (4%, 3 mL) may be applied with a tongue depressor to the back of the throat; patient to gargle and spit
        - Lidocaine (4%, 5 mL at 5 L/min) can be nebulized
        - Although lidocaine (4%, 3 mL) can be applied to epiglottis and top of vocal cords using an atomizer device, the patient will cough during the procedure.
    - Choices for sedation include benzodiazepines, opioids, and agents commonly used for procedural sedations (ie, etomidate, propofol, and ketamine).
        - If time permits, may consider oral administration of benzodiazepines or opioids. Although intranasal administration of these agents is also an option, absorption may be impacted by increased congestion and mucous in the setting of COVID-19.

Acute respiratory distress syndrome (ARDS)

Conservation pearls:

- Optimize ventilator and sedation/analgesic strategies to prevent patient ventilator dyssynchrony prior to considering use of a NMBA.[11]
- In patients with moderate to severe ARDS, NMBAs can be used as needed and should be initially given as intermittent boluses to facilitate ventilation targets.[12]

Detailed information

- Reserve continuous NMBA infusions for patients who have an indication for ongoing paralysis in which intermittent dosing may not suffice:[12]
    - Patients with persistent ventilator dyssynchrony**;** need for ongoing deep sedation**;** prone ventilation**;** persistently high plateau pressures.
    - Consider continuous infusions in patients that have a partial or transient response to intermittent boluses. If patient has had no response to intermittent boluses, it is unlikely NMBs will be beneficial.
- Continuous infusions of NMBAs to improve mortality have only been studied for up to 48 hours in ARDS.[13,14] The benefit to risk balance of shorter or longer NMBA duration is unknown.[12,15]
- In obese patients (BMI $\geq$ 30 kg/m^2), use ideal body weight or adjusted body weight for dosing. There is no preference for one weight strategy over the other.[15]
- If using a fixed-dose strategy for NMBA infusion (ie, cisatracurium) consider a titratable regimen that may reduce excessive blockade and reduce the NMBA dose.[11,16,17]
    - A peripheral nerve stimulator with train-of-four monitoring (TOF) should not be used alone to guide NMBA dose titration. The degree to which clinical goals are being met should guide monitoring and NMBA dose titration.[15]

Alternative agents:

- Nondepolarizing agents (benzylisoquinolinium and aminosteroidal compounds) are the only NMBAs that have been studied in ARDS.[11] Dosing of alternative agents is described in Appendix 1.
- While cisatracurium is the only NMBA that has been evaluated for protective ventilation in ARDS in randomized, controlled trials, the following data exist for use of alternatives:
    - Small, retrospective cohort trial that compared cisatracurium with atracurium in early ARDS - no difference in clinical outcomes (ventilator-free days, ICU length, hospital mortality, improvement of PaO_2/FiO_2).[18]
    - Observational database that compared cisatracurium with vecuronium in patients with a diagnosis of ARDS or at risk of ARDS - there was no difference in mortality, but data favored cisatracurium for ventilator-free days and ICU days.[19]
    - Placebo controlled trial of vecuronium in early ARDS.[15]
- Selection of an alternative NMBA should be based on availability of alternatives and patient specific factors.[20] Potential considerations:
    - If possible, cisatracurium should be reserved for patients with hepatic or renal dysfunction because it undergoes Hoffman elimination and has no toxic metabolites. Cisatracurium is the only NMBA that does not cross the placenta barrier.[11]
    - Atracurium metabolism results in the toxic metabolite, laudanosine. While there is potential for accumulation in patients with renal impairment, laudanosine accumulation is unlikely to cause seizure activity at doses normally used in the ICU setting.[11,15]
    - Atracurium causes histamine release due to its direct action on mast cells. This release may be attenuated by a slower injection rate or by pretreating with H_1 and H_2 antagonists.[15]
    - Pancuronium causes mild to moderate tachycardia and should be avoided in patients with coronary artery disease due to risk of myocardial ischemia, ventricular ectopy, and cardiovascular collapse.[15]

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Appendix 1: Neuromuscular blocking agents used in the intensive care unit[20]

Drug	NMBA Type and category	Time to max blockade (min)	Duration of action (min)	Dose	Elimination	Active metabolites	Comments
Pancuronium	Aminosteroid long acting	2-3	60-100	**Bolus**: 0.05-0.1 mg/kg **Continuous**: 0.8-1.7 mcg/kg/min	Renal: 45-70% Hepatic: 15%	3-OH and 17-OH pancuronium	Vagal blockade, sympathetic stimulation, blocks muscarinic stimulation (bradycardia)
Vecuronium	Aminosteroid, intermediate acting	3-4	20-35	**Bolus**: 0.08-0.1 mg/kg **Continuous**: 0.8-1.7 mcg/kg/min	Renal: 10-50% Hepatic: 35-50%	3-Desacetyl-Vecuronium	Vagal blockade at higher doses
Rocuronium	Aminosteroid, intermediate acting	1-2	20-35 With rapid sequence dose: 60-80	**Bolus**: 0.6-1 mg/kg (1-1.2 mg/kg for rapid sequence) **Continuous**: 8-12 mcg/kg/min	Renal: 33% Hepatic: <75%	None	Vagal blockade at higher doses, weakly blocks muscarinic stimulation (bradycardia)
Atracurium	Benzylisoquinolinium, Intermediate acting	3-5	20-35	**Bolus**: 0.4-0.5 mg/kg **Continuous**: 5-20 mcg/kg/min	Renal: 5-10%, Hoffman elimination	None (toxic metabolite - laundanosine, may accumulate in renal insufficiency)	Histamine release, minimal ganflionic blockade
Cisatracurium	Benzylisoquinolinium, Intermediate acting	2-3	30-60	**Bolus**: 0.1-0.2 mg/kg **Continuous**: 1-3 mcg/kg/min	Renal: 5-10%, Hoffman elimination	None	--
Succinylcholine	Depolarizing agent	< 1	5-10	**Bolus**: 1 mg/kg, dose higher in pediatrics	Plasma cholinesterase	None	Minimal amount of histamine release, muscarinic stimulation (bradycardia) Not used for continuous paralysis

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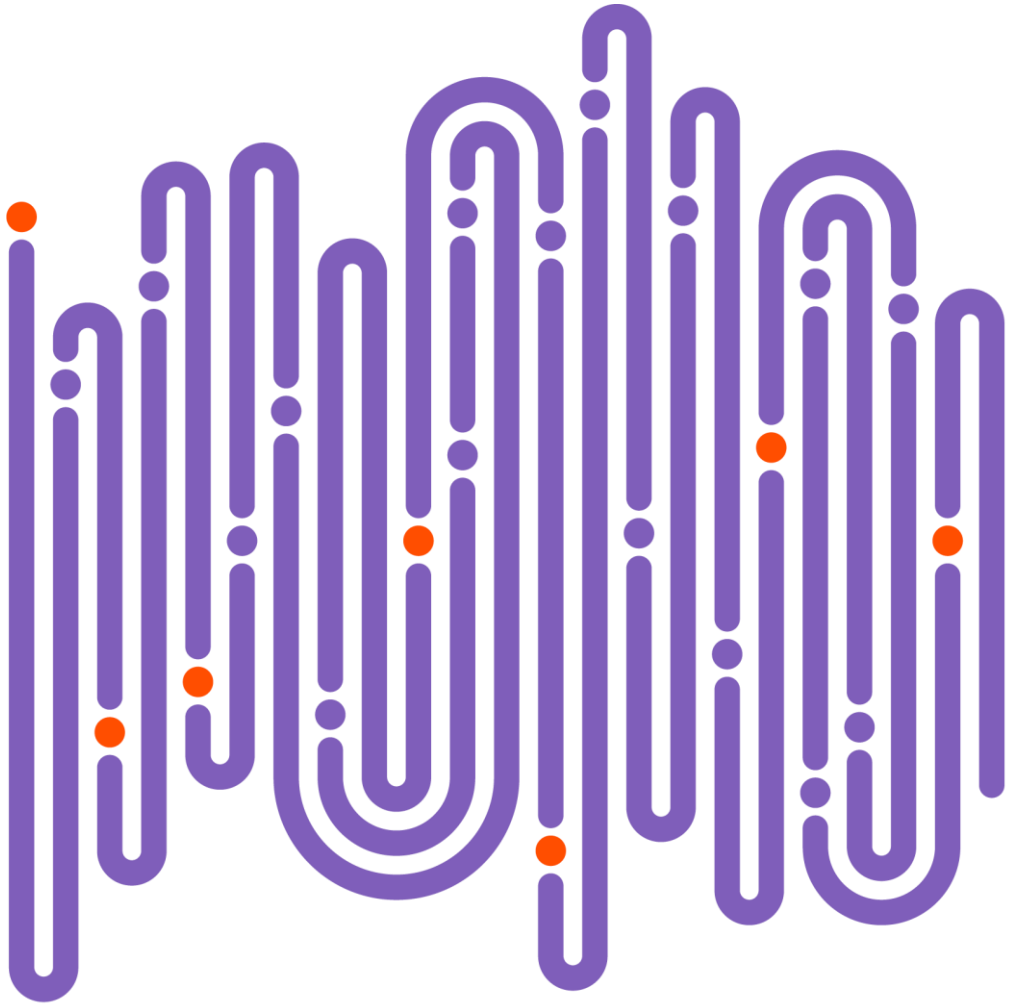

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