

# Improving the safety of neuromuscular blocking agents: A statement from the USP Safe Medication Use Expert Committee

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The United States Pharmacopeia (USP) is a volunteer-based, not-for-profit organization whose mission is to promote the public health by establishing and disseminating officially recognized standards of quality and authoritative information for the use of medicines and related articles for professionals, patients, and consumers. As one of USP's 62 expert committees in the Council of Experts, the USP Safe Medication Use Expert Committee has taken on many activities to improve patient safety with regard to the use of medicines. A key area of focus has been neuromuscular blocking agents (NMBAs) (Table 1), which can be associated with severe patient harm and death.

## NMBAs

NMBAs, also known as paralyzing agents, are considered high-alert medications (those with the highest

**Purpose.** Recommendations of the interdisciplinary Safe Medication Use Expert Committee of the United States Pharmacopeia (USP) to assist health care professionals, manufacturers, and organizations in handling neuromuscular blocking agents (NMBAs) safely and effectively are discussed.

**Summary.** Review and analysis of the USP Medication Errors Reporting Program and MEDMARX program databases showed a continuing risk of patient harm or death due to errors with NMBAs. Medication errors involving wrong concentrations, wrong doses, wrong drugs, look-alike packaging, and sound-alike names, combined with lack of monitoring and communication, have been associated with the use of NMBAs in health care institutions. Serious

adverse events occur when NMBAs are used without adequate safeguards. Recommendations for improving safety were developed through review and discussion of root causes and areas of concern with these medications.

**Conclusion.** Medical errors with NMBAs continue to result in patient morbidity and mortality. Increased awareness and action on the part of all parties involved are needed to improve the safety of this class of medications.

**Index terms:** Concentration; Death; Dosage; Errors, medication; Hospitals; Nomenclature; Packaging; Reports; Skeletal muscle relaxants; Toxicity; United States Pharmacopeia

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risk of causing injury with misuse), because inadvertent use in patients not receiving ventilatory assistance can lead to respiratory arrest, perma-

nent harm, or death. To minimize this risk, the Safe Medication Use Expert Committee developed the following general recommendations:

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Table 1.  
**Neuromuscular Blocking Agents Marketed in the United States**

Generic Name	Brand Name(s) (Manufacturer)	Dosage Strength(s) Available
Atracurium besylate	Tracrium (Hospira)	10 mg/mL (5 and 10 mL)
Cisatracurium besylate	Nimbex (GlaxoSmithKline)	2 mg/mL <sup>a</sup> (5 and 10 mL), 10 mg/mL <sup>a</sup> (20 mL)
Doxacurium chloride	Nuromax (Hospira)	1 mg/mL (5 mL)
Mivacurium chloride	Mivacron (Hospira)	2 mg/mL <sup>a</sup> (5, 10, 20, and 50 mL)
Pancuronium bromide	Formerly Pavulon (Organon)	1 mg/mL (10 mL), 2 mg/mL (2 and 5 mL)
Rocuronium bromide	Zemuron (Organon)	10 mg/mL (5 and 10 mL)
Succinylcholine chloride	Anectin (GlaxoSmithKline) Quelicin (Hospira)	20 mg/mL (5 and 10 mL), 50 mg/mL (10 mL), 100 mg/mL (10 mL)
Vecuronium bromide	Norcuron (Organon)	10-mg vial

<sup>a</sup>Concentration expressed in terms of the drug base.

- Manufacturers should use drug packaging, labeling, and nomenclature conventions to clearly and readily differentiate NMBAs from other medications.
- Hospitals, clinics, and other practice sites should institute special safeguards in the storage, labeling, and use of these agents and should include these safeguards in staff orientation and competency training.
- Health professionals should be on high alert (especially vigilant) whenever an NMBA is stocked, ordered, prepared, or administered.

While basic medication safety practices must be used and reinforced for all medications, this is especially true for high-alert medications such as NMBAs.

### Problems with the use of NMBAs

NMBAs have been mistakenly administered in place of vaccines, antibiotics, and intravenous flush solutions. Storage and use of these agents outside the operating room (OR), pharmacy, and critical care areas increase the opportunity for errors. Look-alike packaging and labeling is not only an issue with manufacturer-supplied vials. Because of the similar appearance and labeling of institutionally prepared syringes and infusion bags, there is a risk of mistakenly administering NMBAs instead of

other sterile compounded medications. Even when patients are receiving mechanical ventilation and NMBAs are indicated, this use can be problematic. Critical care patients may have difficulty being weaned from the ventilator or may incur long-term sequelae because of the NMBA dose or duration of therapy. Drug–drug interactions can also be a problem. In addition, pain and anxiety may be inadequately treated because of the difficulty of recognizing these symptoms in paralyzed patients.

Medication error reports submitted to MEDMARX, USP's proprietary anonymous national medication error-reporting database (a subscription service with over 750 participating facilities), and the USP–Institute for Safe Medication Practices (ISMP) Medication Errors Reporting (MER) program (confidential, spontaneous, and practitioner based) illustrate the harm or high potential for harm that can result from NMBAs. Over the years, MER reports that are shared with ISMP have become the basis of recommendations made by the institute.<sup>1,2</sup>

Reports have included examples of the following types of errors: (1) an incorrect concentration of an NMBA being dispensed or placed in an automated dispensing machine, leading to a wrong dose, (2) an

NMBA being administered via a hand-labeled or unlabeled syringe when another medication was intended, (3) an NMBA being administered when a different medication in a similar-looking vial or infusion bag was intended, (4) an NMBA being administered when a different medication with a sound-alike or look-alike name was intended, (5) an NMBA being administered without appropriate monitoring for effect, and (6) an NMBA being administered despite a physician's order (oral or written) to withhold the dose or discontinue the medication.

**Contribution of manufacturer packaging and labeling to error reduction.** USP and ISMP have advocated manufacturer labeling and packaging standards for NMBAs with the hope that an FDA standard requirement for all products in this class could reduce fatalities and serious injuries due to unintended administration. Practitioner input through a survey of health professionals,<sup>3</sup> as well as feedback from manufacturers, was solicited in the process of developing revised standards for NMBAs that could reduce the risk of medication errors.

The May–June 2003 *Pharmaceutical Forum*, USP's public-comment document for standards, contains a proposal—becoming official on October 1, 2005—that the ferrules and overseals of NMBA products contain the alert "Warning—Paralyzing Agent" if enough room permits, or at least "Paralyzing Agent."<sup>4</sup> A contrasting color should be used for the warning, either black or white, whichever provides the best contrast. To truly differentiate NMBAs from other medications, however, all manufacturers and distributors need to institute standardized labeling, standardized packaging, and distinctive shapes for these products.

**Effect of provider awareness and organizational action on adverse outcomes.** Actions by individual manufacturers are only part of the

solution to improving the safety of NMBAs. Pharmacists, physicians, nurses, and other hospital staff must also implement system changes to ensure safe storage, access, distribution, labeling, and optimal therapeutic use of NMBAs. USP's Safe Medication Use Expert Committee, after reviewing potential and reported failure points in the medication-use process, offers health care practitioners and institutions the following recommendations to reduce the risk of errors.

*Formulary management and product selection.*

- Procurement managers should preferentially select commercial products that have distinctive labeling and packaging to differentiate these products.
- As part of the competitive bidding process, procurement managers should evaluate product labeling and avoid purchasing NMBAs with similar trade dress or an appearance similar to that of other medications that will be used in the institution.
- Pharmacy and therapeutics committees should conduct a failure-mode and effects analysis<sup>5</sup> on all new high-alert medications, including NMBAs, before they are added to the formulary.

*Product storage.*

- Hospital and other personnel should store NMBAs separately from other medications.
- Hospital and other personnel should limit the availability of NMBAs to the pharmacy and patient care areas that routinely care for mechanically ventilated patients.
- Hospital and other personnel should carefully scrutinize (e.g., by conducting a failure-mode and effects analysis) any perceived need to store NMBAs in settings where mechanical ventilation is used occasionally or only emergently, such as emergency departments, procedure and clinic areas, and general nursing units.

*Limiting or controlling access (restricting availability).*

- Practitioners should use sealed “intubation kits” or “anesthesia kits” in areas outside of the OR to restrict access to paralyzing agents until an intubation procedure has begun.
- Practitioners should immediately discard open vials of NMBAs or ensure that the vials are returned to an intubation kit or special storage area after use.
- Practitioners should not dispense NMBAs in unit dose medication carts or send NMBAs to a general nursing unit outside a sealed kit.
- When NMBAs are stored in automated dispensing machines, practitioners should use an isolated drawer (single-item access) rather than a drawer that allows access to multiple products, including nonparalyzing agents. They should consider the use of an on-screen warning prior to removal of an NMBA from an automated dispensing machine.
- Practitioners should consider separate locked storage for refrigerated NMBAs. If this is not possible, a box or other means of sequestering these products should be designed.

*Use of overwraps and auxiliary labeling.*

- All institutionally prepared syringes or infusion containers of NMBAs should contain a clearly visible, brightly colored alert stating, “Warning: Paralyzing Agent (Use Requires Mechanical Ventilatory Assistance).”
- Overwraps should be considered for individual vials of NMBAs stored outside the pharmacy or the anesthesia area. An overwrap can be particularly beneficial if these agents are stored in a refrigerator.
- Medications in unlabeled syringes should not be administered to patients. Preprinted syringe labels—either commercially available or institutionally generated—should be affixed to syringes of NMBAs when the

medication is drawn up, unless the dose will be administered immediately (i.e., in an emergency), without setting the syringe down.

*Implementing and monitoring guidelines for NMBAs.*

- Practitioners should ensure that patient selection, dosing, monitoring, and weaning of NMBAs are consistent with the current evidence and national practice guidelines.<sup>6,7</sup> Practitioners should prescribe adequate sedation along with pain relief, without paralysis whenever feasible, for mechanically ventilated critical care patients.
- NMBAs should not be administered in the critical care setting (for reasons other than placement of an endotracheal tube) without concurrently medicating the patient for pain or anxiety, despite the lack of obvious symptoms or signs.
- Practitioners should monitor the depth of neuromuscular blockade to allow use of the lowest NMBA dose and potentially minimize adverse effects.

*Ordering practices.*

- Practitioners should automatically discontinue all orders for NMBAs when the patient is transferred out of the critical care area. These orders should also be limited to the duration of mechanical ventilation.
- NMBAs should never be used “p.r.n. for agitation” or referred to as muscle relaxants.

*Use of bedside verification and smart-pump technology.*

- Hospital personnel should use technology for improving accuracy, such as bar-code readers to verify product and patient identity before administration. Programmable infusion devices now offer customized settings that meet a hospital's guidelines of selected drug dosages for specific pa-

tient types and specialized clinical care areas. Patient safety features are the factors that most often distinguish one pump from another. A so-called smart pump is an intravenous pump that is programmed to sound an alarm if it is set for other than a recommended dose and rate based on individual patient variables.

*Focused education and practitioner credentialing.*

- Professionals who administer medications in the anesthesia area or OR, critical care area, and emergency department should receive special education and training on the safe handling and dosing of NMBAs (recognizing that use of these agents is not routine for nonanesthesiologists).
- Health care organizations, in conjunction with the medical staff, should outline credentialing and privileging requirements for providers prescribing and administering NMBAs and consider placing all NMBAs in a

formulary category to limit prescribing to those with the experience and qualifications necessary to use these high-risk medications safely.

- Nurses and other professionals who administer medications outside the OR or critical care setting should be trained to recognize NMBAs and to know their mechanisms of action and associated risks.

**Conclusion**

Medical errors involving NMBAs continue to result in patient morbidity and mortality. Increased awareness and action on the part of all parties involved—manufacturers and suppliers, purchasers, and all practitioners involved in the entire medication-use process—are needed to improve the safety of this class of medications.

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