

Neuromuscular Blocking Drugs

IACUP Policy

Approval Date: November 2023

I. Purpose

This policy provides standards to ensure that animals undergoing procedures involving neuromuscular blocking drugs receive proper anesthesia to preserve their welfare. Systemic paralysis is most commonly utilized in neuroscience research to minimize or prevent self-generated movement, such as movement of the ocular muscles during visual experiments. This requires the animal to be paralyzed with a neuromuscular blocking drug (NMBD).

Neuromuscular blocking drugs present a risk to animal welfare by eliminating normal signs of pain or distress. This policy has been developed to ensure that UCSF complies with the *Guide for the Care and Use of Animals*, 8th Edition, and the *Animal Welfare Act and Regulations*.

II. Regulatory or Accreditation Authority

Animal Welfare Act and Regulations, 9 CFR 2.31(d)(1)(iv)(C), Institutional Animal Care and Use Committee - "Procedures that may cause more than momentary or slight pain or distress to the animals will ... not include the use of paralytics without anesthesia."

Guide for the Care and Use of Laboratory Animals, Eighth Edition, p. 123. November, 2013 - "because this paralysis eliminates many signs and reflexes used to assess anesthetic depth, autonomic nervous system changes (e.g., sudden changes in heart rate and blood pressure) can be indicators of pain related to an inadequate depth of anesthesia. It is imperative that any proposed use of neuromuscular blocking drugs be carefully evaluated by the veterinarian and IACUC to ensure the well-being of the animal."

III. Scope

This policy applies to all animals cared for at UCSF administered neuromuscular blocking agents for experimental purposes, both in and outside of centralized LARC care space.

IV. Definitions

Neuromuscular Blocking Drug: Any compound or drug that blocks the neuromuscular transmission causing paralysis of the skeletal muscles. NMBDs are also referred to as paralytic drugs, for example, atracurium or pancuronium.

V. Policy

Considerations for Procedures:

NMBD can be administered only when the animal is adequately anesthetized and an appropriate means of mechanical ventilation is provided. NMBDs provide no anesthesia or analgesia and interfere with standard indicators of anesthetic depth, so their use will only be approved under the following conditions:

1. The use of NMBDs in animals will only be approved in specific situations for which investigators can document the scientific necessity of their use. Use of NMBDs must be described and justified in the protocol and approved by the IACUC.
2. Investigators should confirm that the anesthetic regimen is sufficient to prevent pain and distress associated with the experimental procedure in the absence of the NMBD. Gaseous anesthesia or constant rate infusion of injectable anesthetics is preferred. Maintenance of consistent surgical depth is more challenging using bolus administration of injectable anesthetics such as ketamine and xylazine.
3. All surgical or otherwise potentially painful procedures must be performed under adequate anesthesia prior to NMBD administration. After the surgical or painful portion of the procedure is complete, at least 15 minutes of stable, effective anesthesia is required prior to NMBD administration.
4. The following alterations to physiological variables can indicate that an animal is returning to lighter depth of anesthesia:
 - a. Increase in heart rate;
 - b. Increase in arterial blood pressure;
 - c. Salivation, lacrimation, dilation of pupils;
 - d. Defecation, urination;
 - e. Increase in end-tidal CO₂ on capnograph;
 - f. Muscle twitching, especially around the head (e.g. curling tip of tongue), muscle movement of the limbs
5. Mechanical ventilation must be initiated prior to administration of the neuromuscular blocking drug. Once NMBDs have been administered, the anesthetic level must not be decreased except as described below. **Respiratory support must be continued until the animal is recovered from NMBD.**
6. The adequacy of anesthesia must be assessed and documented. In mammals, this should be accomplished by testing for lack of response to a noxious stimulus, such as a 'toe pinch,' prior to the period during which NMBDs are administered. Baseline heart rate is documented prior to NMBD administration. An increase in heart rate of 20% or greater within 1 minute of the toe pinch may be taken as a significant positive response, indicating that the depth of anesthesia is insufficient to administer NMBD.
7. Parameters, such as core temperature, heart rate, EEG, and end-tidal CO₂, must be monitored continuously and documented periodically to ensure that physiologic homeostasis is maintained during the periods of paralysis (a LARC template is available in [PDF](#) or [excel](#)). Additional parameters that may be considered for anesthesia monitoring to ensure anesthetic depth include electrocardiogram, respiratory rate, respiratory volume, and oxygen saturation. If a volatile anesthetic agent is used, the inspired and end tidal O₂ concentration, N₂O concentration, and agent concentration should be continuously monitored. Regardless of which monitoring method(s) will be used for a study, it must be described in detail in the IACUC protocol. Documentation must be performed at least every 15 minutes during surgical portion of the procedure but may be extended to every 30 minutes during more stable periods after NMBDs have been administered (e.g., during periods of neurophysiological recordings) if approved in the protocol. If animals will be paralyzed for long periods of time (e.g., greater than 4 hours), provision must be made for periodic voiding of the urinary bladder, if applicable and included in the protocol.

8. If animals are anesthetized for prolonged procedures, anesthetic levels may need to be decreased to allow successful neurophysiological recordings to continue. In such cases, NMBD administration must be discontinued prior to decreasing anesthetic level, such that normal muscle and physiologic responses allow assessment of anesthetic depth prior to re-induction of paralysis.

Requirements for proposing NMBD use in the IACUC Protocol:

1. The need for NMBD administration must be scientifically justified.
2. The anesthetic and NMBD regimens and methods of heart rate monitoring and ventilation must be specified.
3. Pharmaceutical grade formulations of NMBD must be used when available unless justified in the protocol and approved by the IACUC.
4. The method(s) that will be used to monitor anesthetic depth during NMBD paralysis must be described, including:
 1. A thorough anesthetic monitoring record (a LARC template is available in [PDF](#) or [excel](#)) for all animals, documenting the dose, time and route that all anesthetics, paralytics, and analgesics are administered;
 2. Monitoring and periodic documentation of physiological parameters appropriate for the species being studied;
 3. Details of the specific parameters to be monitored and frequency of documentation must be included as part of the Animal Use Protocol.

References:

1. Committee on Guidelines for the Use of Animals in Neuroscience and Behavioral Research. National Research Council. (2003). Guidelines for the Care and Use of mammals in Neuroscience and Behavioral Research. National Academy Press: Washington, D.C.
2. Drummond JC, 1996. Use of neuromuscular blocking drugs in scientific investigations involving animal subjects. *Anesthesiology*, 85(4):607-699
3. Guidelines for the use of neuromuscular blocking drugs in anesthetized animals. Animal Care and Use Committee, University of California, Berkeley. <https://acuc.berkeley.edu/guidelines/nmbd.pdf>. Revised 2013. Accessed 30 August 2023.
4. Preparation and maintenance of higher mammals during neuroscience experiments. Report of a National Institute of Health workshop. 1991 Van Sluyters RC, Oberdorfer MD, eds. NIH Publication No. 91-3207.
5. Standards on Monitoring Animals on Neuromuscular Blocking Agents. Institutional Animal Care and Use Committee, University of North Carolina at Chapel Hill. <https://policies.unc.edu/TDCClient/2833/Portal/KB/ArticleDet.aspx?ID=132202>. Revised 5/19/23. Accessed 30 August 2023.
6. University of British Columbia Animal Care Guidelines. <https://animalcare.ubc.ca/sites/default/files/documents/SOP-ACC-04-2016%20Neuromuscular%20Blocking%20Agents.pdf> Revised 2016. Accessed 30 August 2023.