Neuromuscular Blocking Drugs

IACUP Policy

Approval Date: November 24, 2020

UCSF Office of Research
Institutional Animal
Care and Use Program

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, both in and outside of centralized LARC care space.

IV. Definitions

Neuromuscular Blocking Drug: Any compound, 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:

NMBA 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 therefore must be described and justified in the protocol and approved by the IACUC.

2. Investigators should confirm that the anesthetic technique is sufficient to prevent pain and distress associated with the experimental procedure in the absence of the NMBD. Use of injectable anesthetics such as Ketamine and Xylazine can be more challenging because they are unreliable for maintaining animals at a surgical depth for long periods of time. Gaseous anesthesia is preferred.

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, the animal must be maintained without NMBDs at a fixed anesthetic level until physiologically stable. 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 will be taken as a significant positive response, indicating that the depth of anesthesia is insufficient.

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. Documentation must be performed at least every 15 minutes during surgical portion of the procedure but may be extended every 30 minutes during more stable periods after NMBDs have been administered (e.g., during periods of neurophysiological recordings). 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.

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, such that normal muscle and physiologic responses allow assessment of anesthetic depth prior to re-induction of paralysis.

Requirements for Submission of an Animal Use Protocol that Proposes to use NMBA

1. The need for NMBA must be scientifically justified.
2. The anesthetic protocol, NMBA regimen, and methods of heart rate monitoring and ventilation must be specified.
3. Pharmaceutical grade formulations of NMBD may be unavailable but must be used when available, unless justified in the protocol and approved by the IACUC.

A description of the method(s) that will be used to monitor anesthetic depth during NMBA paralysis must be included. A thorough anesthetic monitoring record must be kept for all animals. Physiological parameters appropriate for the species being studied must be monitored and documented periodically. Details of the specific parameters to be monitored and frequency of documentation must be included as part of the Animal Use Protocol.

Adequate Anesthesia Monitoring and Ensuring Adequate Anesthetic Depth

In animals receiving NMBA, the following parameters may be considered for monitoring: electrocardiogram, electroencephalogram, body temperature, respiratory rate, respiratory volume, oxygen saturation, end-tidal CO_2. If a volatile anesthetic agent is used, the inspired and end tidal 0_2 concentration, N_20 concentration, and agent concentration should be continuously monitored. Regardless of which method(s) will be used for a study, it must be described in detail in the IACUC 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 2 Nov 2020.
4. 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 2 Nov 2020.
5. 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.