

EDITORIAL VIEWS

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Use of Neuromuscular Blocking Drugs in Scientific Investigations Involving Animal Subjects

The Benefit of the Doubt Goes to the Animal

IN the course of ANESTHESIOLOGY's manuscript review process, there have been occasional discussions between authors and reviewers regarding the appropriate and ethical use of neuromuscular blocking drugs (NMBDs) in animal subjects. Concern regarding the use of NMBDs in animal subjects is not unique to ANESTHESIOLOGY. The National Institutes for Health's "Guide for the Care and Use of Laboratory Animals"[§] and the Animal Welfare Act^{||} both set forth the principle that NMBDs must not be used to provide "surgical restraint"[§] in lieu of adequate anesthesia. This principal is intended to eliminate experiments in which the use of NMBDs might preclude recognition of inadequate anesthesia by preventing otherwise "awake" animals from moving or trying to escape. The Journal accepts this principal. Nevertheless, questions do arise, and although this issue was addressed in a recent editorial,¹ it was decided that additional published commentary was needed to further clarify the Journal's position.

As in human anesthetic practice, there should be valid indications for the use of NMBDs in experimental animals; this issue takes on a major ethical dimension in those circumstances in which there is a potential that signs of inadequate anesthesia might be masked. Exactly what are these indications? There is unlikely to be difficulty when NMBDs are used to facilitate surgical exposure or preparation in adequately anesthetized animals; however, in this case, use of NMBDs should be confined solely to that phase of the procedure for which they are indicated. Similarly, there are unlikely to be difficulties if the NMBDs are the specific subject of the investigation (since such studies are invariably performed in anesthetized animals). Neuromuscular blocking drugs also may be an important adjunct to

neurophysiologic recording in circumstances where residual electromyographic activity would create an unfavorable signal to noise ratio, or where even a tiny amount of involuntary movement (e.g., a cough) might displace or damage recording electrodes. But what about those experimental circumstances where the investigator believes that the combination of NMBDs with a relatively "light" anesthetic state is necessary? How does one ensure that animals are "asleep"? Some would argue that the monitoring of hemodynamic variables (blood pressure, heart rate, etc.) or the electroencephalogram are sufficient to ensure an adequate anesthetic depth. Others might also argue that maintaining volatile anesthetic concentrations at or just above "MAC-awake" is acceptable. In our opinion, both are probably inadequate, largely because of our limited understanding of the relations between these parameters and "awareness" in experimental animals. In many cases, it is extremely difficult to even define what is a normal blood pressure/heart rate or electroencephalogram in an experimental animal (what constitutes "stress-related tachycardia" in an animal whose resting heart rate is 300 beats per min?). MAC-awake is based on a subject's initial response to commands—Is there an animal equivalent? A better recommendation is based on the approach used by the Institutional Animal Care and Use Committee (IACUC) at the University of California, San Diego and its affiliated VA Medical Center—and by many experienced animal experiments. When the intended use of NMBDs creates any substantial possibility of awareness during paralysis, investigators may find it appropriate to perform (and report in both their IACUC and journal submissions) pilot investigations to confirm that escape behavior does not occur in the circumstances of the intended investigation *in the absence* of the NMBD. Ideally, these experiments should be carried out after consultation with the local IACUC and/or the institution's attending veterinarian.

What constitutes *inappropriate* use of NMBDs? We should all agree that performing surgery on a paralyzed but unanesthetized animal is entirely unacceptable.

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§ Guide for the Care and Use of Laboratory Animals, Health and Human Services, NIH Publication No. 86-23, Revised 1996, pp 58-9.

|| Animal Welfare Act (Public Law 89-544, 1966, as amended, (P.L. 91-579, P.L. 94-279 and P.L. 99-198) 7 U.S.C. 2131 et seq.). Code of Federal Regulations (CFR), (Title 9, Chapter 1, Subchapter A, Parts 1, 2 and 3) p 16.

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Surgery performed with regional/local anesthesia in paralyzed animals is also unacceptable because it does not abolish consciousness. But what about the situation in which paralysis is continued after discontinuing the anesthetic that had earlier been used during surgery? In our opinion, this is also unacceptable, unless limited to very short time intervals, during which the residual effects of the surgical anesthetic would be expected to remain. What about paralysis continuing for several hours during the washout of a long-acting intravenous anesthetic, such as a barbiturate or high-dose opioid? Again, given the known subject-to-subject variation in the clearance of any drug, we believe that the danger of the anesthetic dissipating before paralysis is halted makes this inadvisable, although, in such a situation, if there is believed to be an indication for continued relaxation, pilot experiments such as those suggested earlier would be appropriate.

Does approval by the local IACUC guarantee that a manuscript will be acceptable to ANESTHESIOLOGY? Unfortunately, the answer must be a firm no! Although the Journal requires a statement that IACUC approval was obtained for all animal studies, this does not guarantee acceptability to the Journal. Not all IACUCs have members with a comprehensive knowledge of the effects or appropriate doses of anesthetic agents in all animal species, or familiarity with all relevant experimental methods. The Editor-in-Chief and Editorial Board of ANESTHESIOLOGY must retain the right to reject a submitted manuscript if, in their opinion, the principals stated elsewhere in this document are not met—regardless of the conclusions by a local IACUC. As a relevant aside, the comments earlier concerning IACUC approval highlight the desirability of having anesthesiologists (M.D. or D.V.M.) or other individuals broadly experienced in animal anesthesia as members of IACUCs. These individuals should be appropriately familiar with interspecies variation of both MAC and the potencies of various intravenous agents and will be well positioned to provide important guidance to local investigators.

The preceding statements may appear to some anesthesiologists to be too rigorous a standard. Some will probably contend that investigators performing research using animal subjects are being held to a higher standard in assessing anesthetic adequacy than apply when dealing with humans in the operating room. Some would assert, for instance, that a nitrous oxide/opioid/relaxant technique that is satisfactory in patients in terms of the absence of physiologic respon-

siveness and awareness would be unacceptable because of patient movement if the NMBDs were omitted. Perhaps. *However, inconvenient or not, the contemporary approach is that the benefit of the doubt goes to the animal.* This approach appears appropriate from at least three vantages:

The first is the necessity to assure humaneness. In instances of awareness during surgery, we receive very specific "feedback" from our patients (and from the medical-legal system) to redirect us in our anesthetic practices. No anesthesiologist would continue using a particular technique if five consecutive patients complained of either intraoperative pain or awareness. However, we do not receive the same unambiguous feedback from our animal subjects.

The second is the necessity to assure the relevance of the physiologic observations that evolve from an investigation. As anesthesiologists, we appreciate the importance of minimizing the stress response of our patients. Nonetheless, we have occasionally heard the assertion "I can't use anesthetics (or I must use NMBDs combined with an inadequate anesthetic) because they will distort my results." In almost all circumstances, this is an invalid argument. It may be true that anesthetics will influence results—but it is equally true that the stress associated with paralysis and pain will also influence results, perhaps even more so. If there is a suspicion that the anesthetic may be an important confounding variable, then the investigator should consider comparing the results of experiments with two or three dissimilar anesthetics. Alternatively, he/she should investigate the use of other methods, including awake, chronically instrumented animals (although these raise other ethical issues).

The third is the importance of preserving the research community's important privilege to use animal subjects in biomedical research. Although many of us abhor the stridor with which the animal rights community has assailed the use of experimental animal subjects, we must accept responsibility for assuring that their claims have no foundation in truth. The level of external pressure and scrutiny that have resulted are a reality we must respect. The issues that arise in this context are frequently matters of the adequacy of anesthesia and analgesia (and the use of small rodents as opposed to cats and dogs does not change this issue in any way). As a consequence, journals emanating from the anesthesia community must commit themselves to adhering to appropriate standards in the management of animals, in part because both the public

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and the scientific community will view us as setting those standards.

In conclusion, our treatment of animals must be beyond reproach for the sake of our animal subjects, for the sake of scientific validity and for the sake of preserving our privilege to perform scientifically important investigations. In matters of the anesthetic management of animals subjects, ANESTHESIOLOGY should be seen as a leader. Experience indicates—and our stated policy ensures—that the editorial board will be rigorous in its review of animal investigations, because the standards it sets, like it or not, will be used as guidelines by others.

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Reference

1. Steffey EP: Isoflurane-sparing effect of fentanyl in swine [Editorial]. ANESTHESIOLOGY 1995; 83:446-8