Jerald Silverman, DVM, Column Coordinator

Categorizing insufficient pain alleviation

Every IACUC knows Dr. Hal Hendricks. He's the researcher who tries to push the interpretation of federal regulations to the extreme, and always in his favor. He's the one who argues with the IACUC about issues that are almost meaningless to the ultimate conduct of research but can nevertheless be argued. And so it was this Friday, at the monthly meeting of the Great Eastern University IACUC. Hendricks was obsessed with the idea that a USDA Category E study (pain or distress unalleviated by drugs) would somehow make him a target of the Great Eastern IACUC and every animal rights group in the US. Therefore, he insisted that all animals in his guinea pig surgery study be considered Category D, as originally approved by the IACUC, even though some of the animals had experienced a few hours of unalleviated pain. The fault, as perceived by Hendricks, was with the school's veterinarian and the IACUC, because, he said, he had followed every detail of his approved protocol.

As told by Hendricks and confirmed by the veterinarian, he used the anesthetic and analgesic drugs and dosages recommended by the veterinarian and approved by the IACUC. The surgery was done in his laboratory by trained technicians, and postoperative drug use and clinical observations were dutifully recorded. However, the technicians did not promptly notify the veterinarian that the analgesic drug dosage did not sufficiently alleviate the postoperative pain. When the veterinarian was finally called, he quickly administered additional analgesics and told the technicians that Hendricks should notify the IACUC that the drug dose was being increased for all future surgeries under the protocol. There were no further problems after the adjustment was made.

"So what's the problem?" asked Larry Covelli, the IACUC chairman. "The problem," said Hendricks, "is that I did everything exactly as on my protocol, and now I'm being told that the first animals operated on have to be in Category E because they had pain for a few hours. I read the same Animal Welfare Act regulations you have. They say that if I use the appropriate drugs to treat pain, then the animals belong in Category D. And that's what I did. I didn't see anything that says there has to be 100% freedom from pain. In fact, I didn't see anything that even said the pain has to be alleviated. I did what I was told to do, and now I'm being punished for your mistakes. I want those animals in Category D." Covelli tried, but he could not convince Hendricks that Category E was not the catastrophe that Hendricks believed it to be.

Does Hendricks have a valid point, or is he just making a nitpicking argument? How do you think this issue should be resolved?

RESPONSE

Gap between D and E

Jennifer Lofgren, DVM, MS

The exchange between Hendricks and Covelli highlights a gap in the USDA reporting requirements. Should institutions prospectively report the pain or distress category intended for a study, or retrospectively report the category based on the actual pain or distress experienced? Further, if the institution uses retrospective reporting and finds that animals unexpectedly experienced pain (with or without attempted analgesia), how should the animals be categorized if there was no prohibition to the use of analgesia?

Covelli should explain that there are requirements for the alleviation of pain in the Animal Welfare Regulations (AWRs) and other pertinent regulations. The AWRs, Public Health Service *Policy on Humane Care and Use of Laboratory Animals* and USDA Policy #11 all require that pain or discomfort be limited to that which is unavoidable and that animals showing signs of pain or discomfort are given appropriate relief, unless written scientific justification is provided in the IACUC proposal[1–3].

Hendricks first bases his case on the lack of written requirements for 100% pain relief. The regulations do, however, require that analgesia be appropriate to minimize pain. His second contention is that IACUC approval irrevocably secured his protocol in Category D. Thus, Hendricks argues that prospective categorization is appropriate, whereas Covelli contends that these animals should be retrospectively assigned to Category E. The Animal Welfare Act is worded in the past tense, suggesting that the reported category should represent the animal's actual experience, not the predicted experience outlined in the protocol[4]. Accordingly, categorization should be made independently of the positive intentions of the investigator or veterinary team. This sentiment was reflected in the proceedings of the Definition of Pain and Distress and Reporting Requirements for Laboratory Animals meeting by W. Ron DeHaven of the USDA: "We should ultimately question the effect on the animal—not so much the process, but the end result, the outcome for the animal. If the animal experiences pain and/or distress, then it needs to be put into the appropriate category..."[5]

The IACUC's decision to use retrospective reporting, as in this case, highlights a gap between Categories D and E. USDA Policy #11 defines Category D as a protocol that alleviates pain or distress by using a therapeutic agent (anesthesia, analgesia, etc.)[3]. Category E is defined as a protocol in which pain-relieving medications could not be administered due to IACUC-approved research requirements[3]. Neither definition encompasses the scenario presented here: animals prospectively

categorized as D experienced pain due to insufficient analgesia, but the protocol did not prohibit analgesia.

Identification of an appropriate category for the above scenario seems to be subjective, and no subcategories (e.g., D-2) exist; therefore, we should revisit the intent of categorization[6]. Functionally, the USDA and, by extension, the public are interested in knowing how many animals actually experienced pain[5]. With this objective in mind, we can define Category D as animals that were given analgesia, anesthesia or other pain-relieving treatments such that they remained reasonably comfortable. Category E animals, then, predictably or unexpectedly experienced unalleviated pain of substantial duration and/or severity. Staff entrusted with monitoring research animals should be able to accurately recognize and assess their pain[7]. In this protocol, it is assumed that the technicians were adept at recognizing signs and severity of animal pain and that their judgment was that the level of pain was high enough to warrant contacting the veterinarian. Therefore, if Hendricks' guinea pigs had been given additional analgesia within a reasonable amount of time (as determined by their IACUC) after the signs of pain were observed and their pain had been minimized to allow for reasonably comfortable recovery, all of the animals in the protocol should be categorized as D[4]. If some of the animals experienced substantial pain for an extended period of time before receiving analgesic relief (as recorded during post-surgical monitoring), however, then the IACUC has a defensible position in re-classifying those animals as Category E[4]. Covelli should explain to Hendricks that retrospective category adjustments are ultimately beneficial, as they show that his lab, the veterinary staff and the IACUC were carrying out comprehensive animal monitoring while providing objective assessments for areas of improvement, such as enhanced analgesic protocols or retraining regarding postoperative monitoring and communication with veterinary staff.

1. Animal Welfare Regulations. 9 CFR, Chapter 1, Subchapter A, Part 2, Subpart C, Section 2.31(e), 2.36,b, 5–2.35,b, 7.
2. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).
3. US Department of Agriculture. *Animal Care Resource Guide.* Policy #11. (US Department of Agriculture, Washington, DC, 1997). <http://www.aphis.usda.gov/animal_welfare/downloads/policy/policy11.pdf>
4. Karas, A. & Silverman, J. Pain and distress. in *The IACUC Handbook* 2nd edn. (Silverman, J., Suckow, M.A. & Murthy, S., eds.) (CRC Press, Boca Raton, FL, 2007).
5. DeHaven, R.W. Panel discussion with all speakers. in *Definition of Pain and Distress and Reporting Requirements for Laboratory Animals: Proceedings of the Workshop Held June 22, 2000.* 96 (Institute for Laboratory Animal Research, National Academies Press, Washington, DC, 2000).
6. Karas, A. Pain and distress caused by experimental procedures—is it time for a reality check? in *Definition of Pain and Distress and Reporting Requirements for Laboratory Animals: Proceedings of the Workshop Held June 22, 2000.* 39 (Institute for Laboratory Animal Research, National Academies Press, Washington, DC, 2000).
7. National Research Council. *Recognition and Alleviation of Pain in Laboratory Animals* 51 (Institute for Laboratory Animal Research, National Academies Press, Washington, DC, 2009).

Lofgren is a post-doctoral fellow with the Division of Comparative Medicine at the Massachusetts Institute of Technology, Cambridge, MA.

RESPONSE

To 'E' or not to 'E'

Frank N. Ali, MBA, CMAR, RLATG & Robert E. Faith, DVM, PhD, DACLAM

In reviewing the scenario, we believe the following conclusions and observations can be made. First, Hendricks' protocol was approved as Category D by the IACUC. Second, Hendricks claims that he followed every detail of his protocol, including administering anesthesia and analgesia with the proper dosages as prescribed by the attending veterinarian. Third, the technicians in his laboratory (which have been properly trained) carried out the procedure and administered postoperative analgesics as described in the protocol with proper dosages. All observations were documented, but the technicians did not promptly notify the veterinarian that the analgesic did not fully alleviate the animals' postoperative pain.

The concern here is that if the technicians were properly trained, they should have notified the veterinarian immediately that the animals were experiencing postoperative pain. The fact that they did not suggests that there may be a lack of training.

The veterinarian responded by administering additional analgesic and instructing Hendricks to alert the IACUC that the postoperative analgesic dose for the guinea pigs needed to be increased on all future surgeries. The protocol should be amended to reflect the correct dosage.

The fact remains that the animals were in pain for a period of time. The incident needs to be documented to the IACUC as a reportable incident. The investigator should report what happened, the initial actions taken by the technicians, the reasons that the technicians did not alert the veterinarian immediately if they thought the guinea pigs were in pain and the actions taken by the attending veterinarian. Documentation that the additional dosage of postoperative analgesia alleviates the animals' pain should be provided to the IACUC. Whether the incident is reportable to OLAW should be decided by the IACUC, on the basis of the duration and severity of the animals' pain.

Training should be given to the technicians regarding appropriate post-surgical care for guinea pigs, particularly on recognition of the severity of post-surgical pain and immediate notification to the attending veterinarian. Documentation should also be provided that the proper amount of analgesic was given in future surgeries and that there were no further incidents of pain in the guinea pigs.

Hendricks has a valid point. The decision of the IACUC should be that the guinea pigs remain in Category D with a documented incident of inadequate dosage of post-surgical analgesic and a mandatory retraining of the technicians.

Ali is Assistant Director and Faith was the Interim Director, Office of Laboratory Animal Resources, West Virginia University, Morgantown, WV.

RESPONSE

Show me the regulation

Rhett W. Stout, DVM, PhD, DACLAM

We can all sympathize with Hendricks. Often we follow a set of instructions to the 'T' but still feel that we end up with egg on our face. In my opinion, the system worked and could only be improved by providing more training on the recognition of pain and appropriate responses. Although I have no doubt that

Hendricks is not being punished or picked on, without further clarification by the Great Eastern IACUC, he may have a valid classification question worth considering.

Let's assume the few animals in question experienced unrelieved pain longer than "momentary" or greater than "minor." Do any laws, policies or instructions indicate that we should report such animals in category E? The answer is maybe. Unfortunately, the policies and instructions explaining how to classify animals into column E are not found in one single document. Additionally, policies and instructions are revised sporadically for clarification. The reporting requirement for USDA-covered species originates in the Animal Welfare Act (AWA), section 2.36 (ref. 1). The wording in the AWA is very similar to that found on APHIS Form 7023, used by research facilities for their yearly report. Later, Policy 17 was written to further clarify annual reporting[2]. Policy 17, as originally written or later revised, did not tinker with what seems to be a clear identification of which animals should be included in column E of Form 7023. To my knowledge, there are no other specific instructions originating from the USDA regarding annual reports. Considering the tenor of the regulations above, I can understand Hendricks' position.

The wording in the AWA and on Form 7023 seems to emphasize that the classification of animals in column E revolves around pain or distress, where the use of drugs to relieve pain would interfere with the research. For research institutions, the classification takes the form of a prospective question on a protocol. Retrospectively, an institution may find procedures for which no drug or therapy eliminates pain or distress; animals undergoing such procedures would also be included in column E. The animals at Great Eastern fall into neither category, and interference with research was not the issue in the current scenario. The pain was recognized, albeit late, and rectified. Notably, within the Office of Animal Care and Use (NIH-ARAC Guidelines[3]), clear instructions are provided for filling out APHIS Form 7023. These guidelines specifically indicate that the animals in question should be included in column E of the annual report. I wonder if these guidelines are strictly internal policy or if they constitute common, albeit unwritten, knowledge.

In my opinion, the animals should be left in column D. If Great Eastern has a policy covering the current scenario, that policy should be given to Hendricks. Otherwise, Great Eastern should consider its response at a convened meeting of the IACUC. I would welcome further commentary from the USDA.

1. Animal Welfare Act. 9 CFR Ch.1, 2.36.
2. United States Department of Agriculture. *Animal Care Policy Manual* (USDA, Beltsville, MD, 1997). <http://www.aphis.usda.gov/animal_welfare/policy.shtml>
3. Office of Animal Care and Use. *ARAC Guidelines*. <http://oacu.od.nih.gov/ARAC/index.htm>

Stout is Associate Director, DLAM, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA.

A word from OLAW and USDA

In response to the issues raised in this scenario, the Office of Laboratory Animal Welfare (OLAW) and the United States Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care (USDA, APHIS, AC) offer the following clarification and guidance:

The requirement for submission of an annual report of research facilities, finalized in 1971 (ref. 1), was enacted in order to collect information necessary for USDA to fulfill its responsibilities under the Animal Welfare Act—that is, to show that research facilities were following professionally acceptable standards governing care, treatment and use of animals. Research facilities are required to report the number of animals used in experiments without pain or distress; the number of animals used in experiments involving pain or distress for which pain-relieving drugs were used; and the number of animals used in experiments involving pain or distress for which pain-relieving drugs were not used. Routine procedures (e.g., injections, tattooing, blood sampling) involving some necessary pain and distress need not be reported because the pain and discomfort involved in such procedures are of a transient nature[2].

In July 2000, USDA published a request for comments, recognizing that the current system does not include a means to report certain situations, such as the one described in this scenario, where animals experience pain or distress for a reason other than that the use of anesthetic, analgesic or tranquilizing drugs would have adversely affected the procedures, results, experiments, surgery or tests[3].

Guidance on how to report this type of situation may be found in the *Research Facility Inspection Guide*[4], on page 14.1.3. An animal that experiences an unexpectedly high level of pain due to the research procedures during a study, where the pain is recognized and appropriately treated, may be reported in Column D. Of greater concern is the training issue regarding timely reporting to the attending veterinarian of problems concerning animal health and well-being; as mentioned by the respondents, this needs to be resolved. Failure to monitor animals post-procedurally to ensure well-being and to promptly notify the veterinarian that animals were experiencing postoperative pain constitutes a serious departure from provisions of the Public Health Service (PHS) *Policy on Humane Care and Use of Laboratory Animals*[5]. In PHS-supported animal studies, the PHS *Policy* (IV.F.3.a.) requires institutions to report such incidents and to provide a plan and schedule to prevent their recurrence[5].

1. US Department of Agriculture. Animal and Plant Health Service. 9 CFR Part 2: Animal Welfare Regulations; Final Rule. *Federal Register* **36**, 24917–24928 (1971).
2. US Department of Agriculture. Animal and Plant Health Service. 9 CFR Part 2: Animal Welfare Regulations; Final Rule. *Federal Register* **42**, 31022–31029 (1977).
3. US Department of Agriculture. Animal and Plant Health Service. 9 CFR Part 2: Animal Welfare Regulations; Request for Comments. *Federal Register* **65**, 42304–42305 (2000).
4. US Department of Agriculture. *Animal Care Resource Guide: Research Facility Inspection Guide* (US Department of Agriculture, Washington, DC, 2001). <http://www.aphis.usda.gov/animal_welfare/rig.shtml>
5. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).

Patricia Brown, VMD, MS, DACLAM
Director
OLAW, OER, OD, NIH, HHS

Chester Gipson, DVM
Deputy Administrator
USDA, APHIS, AC