Must potential pain mean category E?

Dr. Raj Subaraman, a noted neurophysiologist, recently moved his lab to Great Eastern University and submitted a protocol using the spared nerve injury model to the Great Eastern IACUC. Subaraman proposed to anesthetize his rats and then expose the sciatic nerve at the point where it trifurcated into the tibial, common peroneal and caudal sural nerves. The first two nerves were transected but the sural nerve was left intact. Subaraman’s research team had done the procedure many hundreds of times previously, and he was able to assure the IACUC that there would be no motor dysfunction in the operated limb. By that he meant that the rat would be able to walk and groom normally and also gain weight normally. In fact, during the first postoperative week, abnormalities (such as increased sensitivity to heat or cold) were found only when specific neurological tests were carried out.

Based on his past experience, Subaraman knew that about one week after surgery, some animals would begin to show clinical signs of neuropathy (nerve degeneration, often with associated pain), and so he routinely began his experimental treatments—the crux of his research—four days after surgery. When the treatments were successful, neuropathy and pain were quite minimal and transient. However, when the Great Eastern IACUC finally approved Subaraman’s protocol, it was with the condition that all of the operated animals would be placed in USDA pain or distress category E (unalleviated pain or distress). Great Eastern University, like many other schools, used the USDA’s pain and distress categories even though it was not required to do so. At Subaraman’s former institution, rats that had undergone surgery but had no (or very minimal) motor dysfunction at any time were placed in category D (alleviated pain or distress) as a consequence of the required surgical intervention. Only those animals that developed clinically apparent neuropathy were retroactively placed in category E. Subaraman thought that was fair, but the Great Eastern IACUC said that because the specific neurological tests were able to detect hypersensitivity to heat or cold during the first few postoperative days, there was a reasonable potential for pain or distress to be present on a continuous or near continuous basis. Although Subaraman argued, it was to no avail. The IACUC would not budge.

What is your opinion? Should all of Subaraman’s rats be placed in category E, even though increased pain sensitivity is recognized only when the condition is artificially provoked by cold or heat, or is it more appropriate to have clinically normal animals in category D and only those with clinical neuropathy in category E?

RESPONSE

Much ado about nothing!

William R. Parlett Jr., DVM, DACLAM

Classify as category D or E? Does it matter to the rats or to USDA? No. For any given manipulation of the rats, the pain category classification will have no impact on them whatsoever. The USDA regulations exclude rats of the genus *Rattus* that are bred for research. So we can assume that the IACUC’s policy is simply to apply the same requirements to all species—a laudable, even if unnecessary, goal.

It matters not whether pain is artificially provoked or unprovoked; it is pain either way. Whether hypersensitivity to cold or heat is painful could be argued, depending on degree of the cold or heat, the duration of exposure and the ability of the animal to freely move away from the source of the cold or heat. Given that at Subaraman’s former institution, only the animals that experienced clinical neuropathy were placed in category E, we can assume that the hypersensitivity, and its detection, in this case does not involve more than slight or momentary discomfort—that is, it is not significant.

Because some of the rats will eventually be classified as category E, and because Great Eastern is not excluding rats from the requirements applicable to USDA-covered species, Subaraman must provide scientific justification that the pain or distress cannot be alleviated. We can assume that Subaraman has acknowledged that some of the rats will experience unalleviated pain or distress and has provided the justification and that the IACUC accepted the justification. Therefore, the procedures are approvable. The only questions are which pain category the rats should be assigned to and the timing of these assignments.

Based on Subaraman’s experience, it is known that some of the rats will experience unalleviated pain or distress. This number or percentage of the total number of rats should be classified in category E from the start. Which position would be preferable to defend: (i) that the rats were initially classified as category D but should have been in category E or (ii) that the rats were initially classified as category E but, based on close clinical evaluation, did not experience unalleviated pain and could be classified as category D?

I suggest the following solution: initially, all the rats should be placed in category E. Close post-operative observation and evaluation by research, veterinary and husbandry staff members...
should be arranged (this should be standard practice). Members of the IACUC could also participate in the post-operative evaluations. The rats that unequivocally appear not to experience any unalleviated pain or distress could retroactively be classified as category D. Furthermore, during the annual review process, based on the outcomes of the evaluations and an established history at Great Eastern, the IACUC could consider whether, henceforth (either by amending the current protocol or in future protocols), a percentage of the total number of rats could initially be placed in category D, and those expected to experience unalleviated pain or distress in category E.

Great Eastern University’s IACUC is overly sensitive to the need to classify these rats into pain and distress category E. The use of such categories is required on Annual Reports for the USDA but is not required by OLAW. Assuming Subaraman’s rats are of the genus *Rattus* and are bred for use in research, they are not covered by the USDA. There is no requirement to include information about these rats on the Annual Report to the USDA, and Great Eastern University would be foolish to do so. The report indicating unalleviated pain or distress would be posted on the USDA’s website and would be subject to disclosure under the Freedom of Information Act (http://www.aphis.usda.gov/animal_welfare/efoia/7023.shtml). This could attract unwanted attention from animal rights activists and protestors.

Great Eastern University should retroactively classify USDA-covered animals into pain category E depending upon their response to experimental treatment. They must carry out this classification effectively each year for the period October 1 through September 30 and accurately report it on their Annual Report to USDA. There is no requirement by either USDA or OLAW to classify animals prospectively into pain category E if only a small number of animals will reach that state and they cannot be identified in advance.

Subaraman has already described the manipulations on the rats in detail, and the treatment he is testing will minimize pain and distress if successful. He has proposed withholding of any other treatment for pain or distress based on scientific justification and has fulfilled the requirement of the Public Health Service Policy on Humane Care and Use of Laboratory Animals. Subaraman has a plan to identify and count any rats that develop clinically apparent neuropathy and to report them to the IACUC for categorization into pain category E. This plan leaves the rats without clinically apparent neuropathy in pain category D, as appropriate.

Because these are not USDA-covered animals, annual reporting of animals in pain categories to any agencies is not required. The IACUC may require an annual accounting as the study progresses, and it should require re-evaluation of endpoint criteria when the protocol is resubmitted after three years.

The ability of the stimulation by heat or cold to elicit hypersensitivity early in the project is irrelevant and should not be considered by the IACUC. Application of heat or cold to the area of concern is not part of the normal husbandry of the rats. This IACUC is hypersensitive!


Wardrip is Chief of Large Animal Clinical Services and Associate Professor in the Department of Surgery, and Langan is the Director of the Animal Resources Center, Attending Veterinarian and Associate Professor in the Department of Surgery, at the University of Chicago, Chicago, IL.

To determine which pain and distress category Subaraman’s experimental rats should be placed in, the IACUC should consider the actual pain and distress that the rats will experience rather than a “reasonable potential for pain.” Our ability to recognize pain in animals varies among species; we rely on behavioral signals as well as appearance to identify when an animal is in pain. According to Subaraman, his research team has done this procedure hundreds of times. He testifies that when the procedure is successful, the rats will be able to walk and groom, will gain weight and will not show any abnormalities except increased sensitivity to hot and cold during specific neurological tests. The Great Eastern IACUC is basing its decision on the potential for pain or distress that may be experienced by the rats, not actual pain or distress. We believe it is more appropriate to place clinically normal rats in category D and to place those that develop clinical neuropathy in category E. Even though some rats will be placed in category D, the protocol should still include strong scientific justification for not providing pain relief to the rats placed in category E.

Because there is potential for the rats to develop clinical neuropathy, post-procedure monitoring should be detailed in the IACUC protocol. We would suggest daily monitoring of the rats for signs of pain including but not limited to signs of clinical neuropathy and more than momentary pain or distress associated with the neurological testing. Observations that could be noted include activity level, weight loss or gain, self-mutilation, guarding behaviors, aggressiveness, locomotion, writhing, piloerection, porphyrin staining, and food and water intake. The IACUC should also require Subaraman to include other ways of managing pain in the rats that develop clinical neuropathy such as using a softer bedding material.
Subaraman’s protocol should indicate the humane endpoints for this experiment. When will the rats that develop clinical neuropathy be euthanized? What will be done if they develop other conditions associated with the procedures or treatments that lead to chronic or intractable pain? Because Subaraman and his research team have done this experiment many times, they should be well equipped to anticipate such conditions and to determine humane endpoints. The IACUC will need to determine how much pain and distress is acceptable and take steps to ensure the animal’s welfare by following up with post-approval monitoring.

We agree with Subaraman that the rats that are clinically normal should be placed in category D and those that develop clinical neuropathy should be retroactively placed in category E. We also believe the IACUC should be diligent in reviewing the protocol for guidelines on post-procedural monitoring and humane endpoints and should follow up with post-approval monitoring of the protocol.


Dabbs is Animal Health Technician and Finlay is Lab Animal Medicine Fellow at City of Hope, Duarte, CA.