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Anesthetics in GEM: Does TBE Make the Grade?

The explosive growth in the use of genetically engineered mice (GEM) was nothing new to Great Eastern University. For several years, researchers at Great Eastern had been using transgenic, knockout, and other mice. As might be expected, the IACUC had previously discussed the use of tribromoethanol (TBE, Avertin), an anesthetic agent often used with GEM. Although there were reports in the literature of possible adverse side effects related to the use of this drug, there were other studies with contradictory findings. After having discussed the issue with the University's veterinarians, the IACUC decided to allow the use of the drug.

For years there were no further questions about TBE. The IACUC, as it did with other anesthetic agents, asked questions about the dosage, route of administration, and volume used, but nothing more. However, this attitude changed when Sylvia Stern, the chairwoman of the IACUC, was examining the policies of the USDA, which help to explain the intent of the Animal Welfare Act (AWA) regulations. She noticed that Policy # 3, "Veterinary Care", stated that investigators are expected to use pharmaceutical-grade medications whenever they are available, unless the IACUC approves a non-pharmaceutical-grade product for reasons of scientific necessity. Stern knew, of course, that laboratory mice did not fall under the regulations of the AWA, but the Great Eastern IACUC had long ago agreed to follow USDA regulations for all species. She decided to raise the issue at the next IACUC meeting.

At the meeting, it became evident that most of the researchers formulated the TBE using the appropriate alcohol and distilled water (obtained directly from the building's distilled water supply), and then placed the resulting solution in a clean but not sterile vial. Most did not filter-sterilize the solution, claiming that it was unlikely that any common pathogen could survive in it. The veterinarians said that they knew of no in-house incidents that indicated any medical problems resulting from any of the preparation methods. The discussion centered around two related issues. First, it was quite obvious that most researchers did not want to change to another anesthetic, because the TBE was effective for them. The second issue was the Committee's own policy to use pharmaceutical-grade drugs when they were available. Clearly, alternative pharmaceutical-grade anesthetics were available, and the IACUC had heard no compelling argument that TBE was the only suitable anesthetic. How would you approach the problem facing the Great Eastern IACUC?

Take It Slowly

Adrienne E. Schucker, DVM

Great Eastern's decision to provide the highest quality veterinary care for all species is commendable. Resistance of investigators to a change of their anesthetic regimen is understandable, especially if they have been using TBE for the past 30 years. Therefore, a moderate approach when handling the IACUC's request to adhere to the USDA's Policy # 3 on veterinary care is advisable, keeping in mind the desired end result of compliance with regulatory requirements as well as a high standard of veterinary care.

Regulatory guidelines directly and indirectly indicate that the use of chemical-grade compounds is not appropriate when alternative pharmaceutical-grade drugs are available. USDA's Animal Welfare Act, Policy # 3 states that chemical-grade compounds should only be used if scientific justification is provided by the investigator, and that 'cost savings' is not an adequate justification. Policy # 3 was written as explanatory guidance for AWA 9 CFR, Part 2 Sections 2.31 and 2.33, which requires the use of "appropriate sedatives, analgesics or anesthetics" and that "[e]ach research facility shall assure that the attending veterinarian has appropriate authority to ensure the provision of adequate veterinary care...." The regulations as explained by Policy # 3 indicate that the use of chemical-grade compounds for an anesthetic is not adequate veterinary care. The Public Health Service *Policy on Humane Care and Use of Laboratory Animals* (PHS *Policy*) addresses the use of chemical-grade compounds by requiring that Assured Institutions have absolute compliance with AWA regulations, 9 CFR subchapter A (ref. 1). The Office of Laboratory Animal Welfare (OLAW) also repeatedly refers to the AWA and the PHS *Policy* in the *IACUC Guidebook*, stating that the IACUC veterinary review must ensure that anesthetic use is "in accordance with established veterinary medical and nursing practices[2]."

Given that regulatory guidelines seem to be supportive of Great Eastern's decision to apply Policy # 3 to all species, the IACUC could use a moderate approach that would address the immediate concerns regarding the use of TBE while easing investigators into regulatory compliance. The IACUC could link implementation of the policy to protocol renewal. One protocol renewal cycle would allow investigators to work with the veterinary staff to achieve a comfort level with a different pharmaceutical-grade anesthetic, such as ketamine and xylazine. This would also be the time for investigators to research and detail scientific reasons for not using alternatives, such as changes in mortality or fertility rates experienced with the use of