

University of Utah Cases
Expert Opinion of Dr. Ingrid Taylor, DVM

Introduction

I received a Doctor of Veterinary Medicine (DVM) degree from Washington State University in 2006. I have 8 years of experience in general clinical, emergency, and critical care practice. I served as a U.S. Air Force Public Health officer, where I managed the infectious disease control and public health programs for a base population of approximately 5,000 people. This work included providing medical care to companion animals, military working canines, and Border Patrol canines.

I have reviewed records related to three separate incidents at animal experimentation laboratories connected with the University of Utah. Each of these incidents were reported by the University to the National Institutes of Health's Office of Laboratory Animal Welfare (NIH/OLAW) as a "noncompliance" with federal guidelines on the humane treatment of animals. The records I reviewed include narratives and representations offered by laboratory staff and University administrators regarding the incidents in question.

Based upon this information and my past experience and expertise as a veterinarian, I believe that the animals involved in each of these incidents experienced unnecessary pain and suffering, and that additional problems went unnoticed by the University and OLAW officials. Much of this pain and suffering was a direct result of poor decision-making and negligence on the part of University laboratory personnel and officials. This reflects a systematic failure of the oversight of research programs at the University of Utah. I explain in further detail below.

OLAW Case 'R' - Two rabbits suffer a "prolonged" euthanasia

1. Per the *AVMA Guidelines on Euthanasia*, rabbits that are already under anesthesia may be euthanized by anesthetic gas. Verification of death by bilateral thoracotomy is also acceptable per the *Guidelines*. The use of the urethane was not acceptable.
2. The respiratory rate of 80 bpm in the report is not a slow, deep rate for a rabbit, as claimed. The average respiratory rate for a rabbit is 30-60 bpm. The University represented that this rabbit was larger than normal, which suggests that his or her resting respiratory rate would be on the lower end of that spectrum. An elevated rate of 80 bpm actually indicates the rabbit was experiencing a heightened state of arousal, and was under an inadequate plane of anesthesia when the intra peritoneal (IP) injection of urethane was given. Depending on the time separation between the administration of ketamine/xylazine and the maintenance under gas anesthesia, due to the inadequacies of the chamber the rabbit could have reached an inappropriately light level of anesthesia. Thus, the rabbit likely suffered pain and distress.

3. Urethane has a wide range of unacceptable side effects in animals, including causing problems with glycemic regulation that are applicable to recovery procedures with the drug. Its use is well below the veterinary standard of practice. The *Guidelines* list urethane as an “unacceptable method” of euthanasia for animals in laboratories, under any conditions. It is carcinogenic and absorbs through the skin, which also calls into question the safety of its use by laboratory personnel.

OLAW Case ‘S’ – A marmoset died post-operatively following significant deviations from the IACUC-approved protocol

An adult marmoset was maintained under anesthesia for 14 hours without a patent IV catheter and IV fluid therapy. Anesthetic and paralytic drugs were administered improperly, and monitoring and post-recovery therapy was inadequate. Painful procedures were performed without adequate pain management.

1. Maintaining an animal under anesthesia without a patent IV catheter is only acceptable for quick procedures (20-30 minutes) that are not invasive or require a deep plane of anesthesia. In this case, the marmoset was maintained under a combination of isoflurane gas and ketamine for 14 hours without a catheter.

2. An IV catheter is important for the safety and health of an animal under anesthesia. Without it, emergency resuscitative treatment, analgesics, additional anesthetics, and drugs and fluids needed for physiological support cannot be effectively administered. IV fluids do not just provide hydration—they assist in maintaining blood pressure and blood volume, and prevent hypoperfusion of organs. In fact, hydration, while important, is *not* the most important function performed by IV fluids under anesthesia. IV fluid therapy corrects ongoing fluid losses, supports cardiovascular function, and maintains blood pressure and body fluid volume. Under anesthesia, blood flow is preferentially shunted to important organs like the brain, heart and lungs. Organs such as the liver, kidneys, and gastrointestinal tract receive less blood flow in this protective mechanism. In prolonged anesthesia, this protective blood shunting combined with low blood pressure can end up harming other organs of the body. Kidneys, in particular, are vulnerable to injury and damage from lack of blood flow and oxygenation. IV fluid therapy mitigates this by restoring blood volume and assisting in normal blood flow, and helps to protect the kidneys and other organs. Subcutaneous fluids do not perform the same function—the fluids must be given IV for this protection. Because an animal under anesthesia often experiences reduced blood pressure and hypothermia, subcutaneous fluids take longer to absorb and are not used efficiently by the body. Repeated administration of subcutaneous fluids may even contribute to hypothermia and result in unabsorbed pockets of fluid, which can cause tissue damage and necrosis.

3. University documents indicate that experimenters intended to administer sufentanil, an opioid analgesic, via the IV catheter. Because they failed to insert this catheter, the experimenters performed painful surgeries, including skin incisions, skull thinning, and craniotomies without IV administration of this analgesic. Painful stimulus can cause an animal to rapidly ascend to a lighter plane of anesthesia that may necessitate immediate

correction. Any drugs injected subcutaneously or intramuscularly will take at a minimum 10-20 minutes to take effect. In a hypovolemic and possibly hypothermic animal, this will take longer because normal circulation is impaired. There was no way the experimenters could effectively control anesthetic depth and ensure consistent unconsciousness in this animal.

4. The experimenters administered a paralytic drug by improper route and without the ability to control anesthetic depth. Rocuronium bromide is not labeled for intramuscular (IM) injection, only IV, so the absorption and duration of effect of IM injection are unknown. Some drugs are not appropriate for IM injection because they don't effectively absorb, or can cause significant pain and tissue damage. Without a means to control anesthetic depth (isoflurane had been stopped at this time), a paralytic drug can cause suffering and trauma in an animal, as they can be aware but unable to react or indicate consciousness. It is inhumane to administer a paralytic drug without being able to verify and control anesthetic depth.

5. The experimenter reported that the monkey was "too deeply anesthetized" with a CO₂ level of 23, but then proceeded to administer an additional "half-dose" of ketamine and continue isoflurane anesthesia. A normal CO₂ level for anesthetized animals is around 35-45 mmHg. A CO₂ level of 23 indicates hyperventilation and demonstrates that the monkey was experiencing severe and dangerous effects under anesthesia. This situation should have been investigated and corrected. Low CO₂, or hypocapnia, may indicate low cardiac output, impending respiratory or cardiac arrest, or equipment malfunction such as a dislodged or displaced endotracheal tube. The detrimental effects of hypocapnia include reduction in venous return, underfilling of the right heart, cardiac arrhythmias, bronchoconstriction, leakage of small lung vessels, decreased cerebral perfusion pressure, and cognitive dysfunction that lasts for days following the surgery.¹ While the procedure should not have proceeded in the first place without an IV catheter, at this point the monkey should have been recovered. There was no feasible way this situation could be corrected with the methods the experimenters were using during the procedure. It is extremely likely that prolonged hypocapnia contributed to the marmoset's death.

6. The monkey received ketamine/xylazine as premedication, then two full doses of ketamine/xylazine approximately 40 minutes apart, then a half dose of ketamine approximately two hours later. Although not clarified in the report, presumably all injections were given IM. The specific doses given were not noted. IM injections of ketamine are painful, and ketamine can cause respiratory depression and prolonged recovery at normal doses. At higher doses these effects can be increased. Ketamine does not suppress the pinnal, pedal, corneal, laryngeal, and pharyngeal reflexes and maintains muscle tone, so assessment of anesthetic depth on ketamine alone is difficult. The experimenters grossly misused ketamine in this procedure, and likely increased this monkey's suffering due to the improper use of this drug. Ketamine is approved in primates for restraint,² although commonly used as an induction agent for general

¹ Way, M., & Hill, G.E, (2011). Intraoperative end-tidal carbon dioxide concentrations: What is the target?" *Anesthesiology Research and Practice*, vol. 2011. doi:10.1155/2011/271539

² Plumb, D. (2015). *Plumb's veterinary drug handbook*. 8th edn. Wiley- Blackwell, 2015

anesthesia. It is not intended to be used alone for general anesthesia, and in fact this type of use is contraindicated.² Increasing the dose of ketamine increases the duration of anesthesia, but not the anesthetic depth, resulting in prolonged recovery.

7. Pain medication was not given for painful procedures. The experimenters performed skin incisions, skull thinning, and craniotomies without administering analgesics. Ketamine/xylazine have limited analgesic properties, and ketamine's role in preventing central nervous system desensitization (its only pain modulating property) is effective only in the presence of pain medications. It is questionable whether this effect even occurs with IM injections.³ The procedures were conducted under isoflurane gas only, which has no analgesic properties. The experimenters did not administer pain medication, buprenorphine (0.01 mg/kg subcutaneously) until nearly an hour after the procedures concluded. This was well beyond the window needed to control pain. At this stage in the procedure, the central nervous system was likely already sensitized, a phenomenon known as 'pain wind-up'. As a result, this monkey likely woke up in pain, and the pain would be harder to control because pre-emptive analgesics were not given. Even when an animal is unconscious, he will experience pain if proper pain management does not block the painful stimulus, which includes management before, during, and after the stimulus. Thus, the experimenters' assertion that inadvertent pain was unlikely in this event is false.

8. The experimenters claim that the dose of buprenorphine made the monkey lethargic. However, it is more likely that pain, organ hypoperfusion, prolonged hypoxia and hypothermia, cognitive impairment, and hypovolemia caused the monkey's lethargy rather than the very low dose of buprenorphine given.

9. Post-operative care was inadequate and contributed to the suffering of this monkey. The monkey exhibited signs of hypothermia post-operatively, and the experimenters failed to properly warm and monitor body temperature in the post-operative period.

10. The experimenters administered subcutaneous fluids twice post-operatively. This may have contributed to the monkey's hypothermia, and the fluids likely were not absorbed effectively due to poor perfusion. The monkey was likely suffering from combined hypothermia, dehydration, and hypovolemia in the hours following the anesthetic procedures.

11. Hypothermia, dehydration, and poor perfusion cause severe discomfort. Hypothermia causes shivering, mental confusion, muscle contractions, slow, weak pulses, lethargy, loss of coordination, and possibly convulsions. Dehydration can cause lethargy, headache, nausea, dizziness, rapid heart rate, mental confusion, low blood pressure, and possibly seizures and coma. Hypovolemia can cause rapid heart rate, low blood pressure, weak pulses, cold skin, and loss of consciousness.

³ Personal communication with veterinary anesthesiologist. (2017). Western Veterinary Conference. Reno, Nevada.

Conclusion:

While this monkey was likely unconscious for most of the anesthetic procedures, he most certainly suffered as a direct result of the actions of the experimenters, who caused his death due to improper administration of anesthetic drugs, failure to administer proper physiological support during and after anesthesia, failure to maintain body temperature, failure to correct the serious ventilation issue of hypocapnia, and failure to provide adequate analgesia for painful procedures. This resulted in a prolonged and inhumane death.

OLAW Case 'V' – A lamb died following an unapproved pulmonary function test

In this case, a pulmonary challenge test was given, which involved the administration of methacholine and then albuterol to a two-month old lamb. According to the report, 2-3 minutes after albuterol was given, the lamb suffered labored breathing and cardiac arrest. Prior to the test, the lamb was given lorazepam. Doses of drugs are not disclosed in this document, so I cannot comment on the appropriateness of the drug dosages.

I noted the following concerns:

1. It is poor practice and highly questionable to have the Principal Investigator (PI) who was involved in the wrongful death conduct the necropsy and determine cause of death. This gives the PI an opportunity to misrepresent or even destroy evidence from a necropsy. To provide meaningful oversight and accountability, a qualified veterinarian not affiliated with the research team should perform the necropsy and determine cause of death.
2. The experimenters claimed that the lamb felt no pain because lorazepam was administered prior to the test. Lorazepam is an anti-epileptic and anxiolytic medication that has no pain management properties. It is appropriate as a sedative, but not an analgesic. Thus, the lamb would have still experienced pain and discomfort, but the sedative may prevent an overt and normal reaction to the pain. Lorazepam can cause cardiac arrhythmias when administered rapidly IV, and is contraindicated in patients with severe respiratory insufficiency, which was induced in the lamb during the pulmonary challenge test.
3. Methacholine is not used in veterinary medicine, but is given to animals in experimental respiratory challenge tests. Therefore, current veterinary formularies do not contain information on appropriate dosing and use of this drug. In experiments on sheep, aerosolized methacholine increases tension of the trachealis muscle by 58% and increases airway resistance, via bronchoconstriction, by 183%.⁴ Increased airway resistance can affect lung perfusion, and increase the amount of work the heart has to perform to pump blood to the lungs. This medication can cause cardiac arrhythmias, and is contraindicated

⁴ Wagner, E., & Jacoby, D. (1999). Methacholine causes reflex bronchoconstriction. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, 86(1), 294-7.

in patients with underlying heart disease. Administration of this medication causes discomfort by inducing wheezing and shortness of breath. If this medication was overdosed, or the lamb had an underlying cardiac disease, it is likely that this drug contributed to his death.

4. Albuterol is a drug used in veterinary medicine, mainly in dogs, cats and horses. There is no dosing information in current formularies for sheep. Albuterol is a bronchodilator with effects occurring within five minutes. According to the report, the lamb experienced labored breathing and cardiac arrest within 2-3 minutes after breathing albuterol for six minutes. Albuterol can cause cardiac arrhythmias, and is contraindicated in patients with underlying heart disease. Given the timing of the death, it is likely that either the albuterol or the combination of drugs given caused the cardiac arrest.

5. The PI states that the death was due to sudden cardiac arrest due to the time separation between the cardiac arrest and methacholine administration, but if the lamb's heart was not monitored during that time, an arrhythmia could have already been present, and it is equally likely that death was due to the administration of drugs during the pulmonary challenge test.

All of the above opinions were derived from the representations made by University personnel and experimenters. As new or additional information comes to light, these assessments may be modified.

Sincerely,



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