Recognition and Alleviation of Pain and Distress in Rodents and Rabbits Used in Biomedical Research

Animals used in biomedical research should never be allowed to experience expected pain or distress when analgesic or anesthetic relief would not interfere with the scientific results. The goal of this document is to provide information to investigators, veterinarians, animal care staff, and the animal care and use committee (ACUC) members for use in their deliberations on the issues of recognizing that the paucity of scientific literature on analgesic relief in rodents and rabbits precludes the development of a definitive document at this time. Rather than summarize current scientific literature, the intent of this document is to offer guidance on how to recognize pain and distress in these species, and to provide recommendations on the incorporation of analgesic use into the design and conduct of animal experiments.

Background

The .S. Public Health Service (PHS) Police for Humane Care and Use of Animals (PHS, 1986) requires pain and distress in rodents and rabbits used in animal study proposals (ASP) be addressed. It is the legal and ethical responsibility of investigators, veterinarians, animal care staff, and the ACUC to be aware of the potential for animal pain and distress when conducting animal studies and to observe the animals and eliminate the pain or distress when possible. PHS Police also requires that alternatives be investigated for procedures that induce pain.

The investigator is responsible for addressing any pain and distress potential associated with experimental manipulation. The ASP must contain a description of the measures to be taken to recognize and alleviate that pain. A scientific justification is required when predicted pain cannot be relieved. Compliance with this requirement necessitates that the investigator understand how animal subjects might exhibit pain or

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distress. When determining the presence or absence of pain, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals (U.S. Government Principles For the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training). Likewise, the responsibility of the veterinarians and the animal care staff is to assist the investigators in recognizing pain and distress in subject animals and to offer suggestions on elimination and alleviation methods.

ACUC members are responsible for reviewing animal study proposals for potential pain and distress issues. ACUC members must be assured that the investigators have addressed this subject adequately and that experimentally induced animal pain and distress are minimized.

Pain and/or Distress Recognition in Rodents and Rabbits

Pain and/or distress can manifest itself in many ways in rodents and rabbits. Obvious signs of pain in animals such as lameness an tissue inflammation are easy to recognize. Most signs of pain or distress in rodents and rabbits, however, are quite subtle. Developing an understanding of an animal's normal behavior and appearance is key to identifying the abnormal. Generally, rodents and rabbits are relatively sedentary during normal daylight hours, and quite active during the night. A healthy rodent or rabbit will generally appear alert, well-groomed, eat and drink normal volumes, and when appropriate, interact socially with others of its species. Knowledge or "normal" behavior in these species enables the investigator to notice both obvious and subtle changes which may suggest the presence of pain (see Table 1).

One of the most quantifiable signs of pain in any animal is decreased food and water consumption. This subtle sign may only sometimes be detected through careful, periodic monitoring of an animal's body weight. Another subtlety is that an animal in pain or distress might merely look slightly unkempt, such as ruffled hair coat. An animal may have a glazed or distracted appearance in its eyes. An animal may direct more than usual attention to the cause or location of its pain or distress. Gentle manipulation of the animal may illicit an otherwise undetectable protective response. Difficult to observe changes in respiratory patterns can also be a sign of pain or distress. In rats, a slight reddish (porphyin)-stained discharge about the eyes and nose can be an indication of pain or distress.

When in pain or distress, an animal's normal behavior can become strikingly altered. The animal may act withdrawn or reclusive, and exhibit abnormal posture or ambulation. It may become listless, immobile, hyperactive, agitated, or aggressive. Food and water consumption as well as urination or defecation patterns may change. Stereotypic activity, such as reluctance to move or self-mutilation may develop.

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Animals in severe acute pain may flail about, struggle, or experience abnormal muscle spasms. Along with behavioral changes, pain an distress expression may result in abnormal vocalizations or abnormal facial expressions. A rat or mouse may squeal, groan, grunt, or whine. Rabbits sometimes scream, growl, squeal or become aggressive. Vocalizations, however, are not definitive and reliable indicators of pain or distress in every individual animal. Its absence does not necessarily indicate the absence of pain or distress.

Certain physiological and biochemical changes can help investigators determine if pain or distress is experienced by an experimental animals. An investigator might monitor his animals for abnormally dilated pupils, elevations in blood pressure, heart rate, or plasma glucocorticoid levels. Measuring such changes often requires invasive techniques or specialized equipment, however, and the data collected can frequently be difficult to interpret in the context of experimental procedures.

Another method of assessing the presence of pain and distress in animals is to administer an analgesic and observe for signs of alleviation (see Table 2). If an animal's behavior "normalizes" then it can be assumed that pain was present and that the analgesic administration was beneficial.

In summary, animal pain or distress can manifest itself in a large spectrum. It is important that animal's be monitored for signs of pain and distress and they be eliminated whenever possible.

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ANIMAL RELATED RESPONSES ASSOCIATED WITH PAIN OR DISTRESS

Behavioral

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Aphagia/hyperphagia/pica	
Self-imposed isolation/hiding	
Reduced awareness/response to stimuli	
Lack of libido/ability to reproduce	
Immobility, "freezing" position/crouching	
Agitation/restless sleep	
Head shaking	
Hissing, spitting, biting/growling	
Grimacing/facial expression (static suspension, fullness, spread)	
Crying, whimpering, squealing-plaintive pain reaction	

Adipsia/polydipsia Self-mutilation, gnawing at limbs Lack of care of body surfaces Tearing, lack of blinking reflex Attempt to escape/avoid Exaggerated startle response Twitching, trembling, tremor Choice of cooler surfaces Lethargy/apathy/listlessness/continuous sleep

Physiologic

Hyperalgesia	Diminished, slow or absent reflexes
Penile protrusion	Erected, matted, or dull hair
Unsteady gait	Paralysis/paresis/hyperesthe
Muscle rigidity, lack of muscle tone	Tail lashing/tail erect/tail close
Ears flattened	Positioning to relieve pressur
Ocular discharge/nasal discharge	Body drawn in or maximally extended
Pupillary dilation	Dehydration/sunken eyes/ski
Sweating	Changes in urine color and/or
Change in body odor	Irregular feces (volume, dryne
Vomiting/diarrhea	Rapid, shallow breathing
Weight loss/weight gain	Change in heart rate
Salivation	Panting/shivering/change in t
Convulsions	Swelling/edema/inflammation

Erected, matted, or dull hair
Paralysis/paresis/hyperesthesia
Tail lashing/tail erect/tail close to body
Positioning to relieve pressure on pain area
Body drawn in or maximally extended
Dehydration/sunken eyes/skin tenting
Changes in urine color and/or volume
Irregular feces (volume, dryness, color)
Rapid, shallow breathing
Change in heart rate
Panting/shivering/change in body temperature
Swelling/edema/inflammation/suppuration

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