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ISM-VET-14 啮齿动物止痛方案兽医推荐

Veterinary Guidance: Analgesic Plans for Rodents

目的 GOAL:

确保接受手术治疗的啮齿动物的疼痛适当缓解。对疼痛管理的考虑必须包括非药物的支持以及药物制剂的提供。兽医工作人员可以就疼痛和痛苦迹象的识别提供指导，鼓励在方案设计阶段进行进一步的兽医咨询。无论使用何种疼痛管理策略，动物评估频率确保充分，以确定镇痛计划的适宜性。评估啮齿动物的疼痛是很困难的，因为它们通常会减少与疼痛相关的行为，除非疼痛使其丧失能力。动物可能表现出“正常”的行为，作为避免捕食的固有反应。临床迹象表明啮齿动物的疼痛包括但不限于嗜睡、粗糙的皮毛、缺乏梳理和隔离。这种对特殊表情，面部紧张、鼻部隆起和耳朵位置的评估，是评估啮齿动物疼痛的另一种方法。Ensure proper pain relief to rodents undergoing surgical manipulations. Considerations for pain management must include both non-pharmacologic support as well as the provision of pharmacologic agents. The veterinary staff can provide guidance on recognition of signs of pain and distress and further consultation during the project design phase is highly encouraged. Regardless of the pain management strategy used, animals must be evaluated at sufficient frequencies to determine the appropriateness of the analgesia plan. Assessing pain in rodents can be difficult as they typically minimize pain-associated behaviors unless the pain is incapacitating. The animal may show “normal” behavior as an inherent response to avoid predation. Clinical signs suggestive of pain in rodents include but are not limited to lethargy, rough coat, lack of grooming, and isolation. The rodent grimace scale[20], which considers assessment of orbit tightening, nose bulge and ear position, is an additional way to evaluate pain in rodents.

定义 DEFINITIONS:

疼痛 Pain: an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Unless the contrary is established, procedures that may cause pain or distress in human beings should be considered to cause pain or distress in animals. [3]

止痛 Analgesia: absence of pain in response to stimulation, which would normally be painful.

止痛药 Analgesic: drug utilized to induce analgesia

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术前止痛 **Pre-emptive analgesic:** analgesic interventions used prior to a painful event such as a surgery. The use of pre-emptive analgesia prevents sensitization of the pain pathways, and therefore is more effective in improving animal comfort than post-inductive analgesia.

术后止痛 **Post-inductive analgesic:** analgesic interventions used once signs of pain are recognized. Once pain is present, the pain receptors have already been stimulated and hyper-sensitized, thereby requiring more intervention (analgesics) than pre-emptive treatment.

减轻啮齿动物疼痛的护理指导标准 Standard of care guidance for alleviation of pain in rodents:

非药物干预措施应包括:Non-pharmaceutical interventions should include:

- Gentle handling of the awake rodent as well as gentle manipulation of the tissues intraoperatively to minimize tissue trauma
- Appropriate wound closure including sufficiently spaced wound clips or suture with knots that are secure but not overly tight
- A warm dry environment during recovery from anesthesia to prevent hypothermia
- Maintaining a quiet environment during recovery to minimize external stress
- Ensuring the animal has easy access to food/water (rearing up to food bin may be difficult depending on the location of the surgical incision)
    - Mash (3 food pellets + water in a petri dish) or other nutrient based support such as boost or diet gel (Clear H2O products) placed on the cage floor in a dish and/or
    - Hydrogel (Clear H2O product) or water bottle with a long sipper tube
- Group housing for socially compatible animals following recovery from anesthesia
- Ensuring enrichment such as a nestlet is present, and utilizing a soft bedding material if a ventral incision is present

药物干预措施应包括:Pharmaceutical Interventions should include:

- Appropriate analgesic use as described in the IACUC protocol based on the anticipated level of pain that might be induced by the experimental procedure.
- Ongoing evaluation of the effectiveness of the analgesic plan to ensure pain/distress is effectively alleviated. The veterinary staff should be consulted if the animal exhibits signs of

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pain/distress which are not alleviated by the pre-approved plan as described in the IACUC protocol. Alternatively, if pain cannot be relieved, humane euthanasia may be warranted

TABLE 1: Analgesic guidance based on anticipated pain level

疼痛水平 **Level of Pain or Distress**	轻度 **Mild**	中度 **Moderate**	重度 **Severe**
建议用药 **Suggested pharmacologic analgesia plan**		Perioperative opioid (1-2 doses) and 3 days of NSAID analgesia	Opioid + NSAID for 3 days +/- local analgesia
不同级别示例 **Examples of procedures in each category**	Tail clipping at 21 days of age or greater, trocar implantation of tumor cells	Ovariectomy, intracerebral implantation, osmotic minipump implantation	Thoracotomy/MI creation, abdominal surgery with organ manipulation (i.e. cannulation

NSAIDS (Non-Steroidal Anti-Inflammatory)

Function by inhibiting inflammation and the production of kinins and prostaglandins. They have varying degrees of effectiveness as antipyretics, analgesics and anti-inflammatory agents. More selective NSAIDS such as (carprofen and meloxicam) can alleviate acute pain, such as that produced by surgery.[8] In addition, such agents have minimal side effects caused by COX-2 specific inhibiting agents and provide a longer duration of effect thereby minimizing dosing requirements. In a research setting, consideration should be made when evaluating inflammatory, infectious disease or coagulation models. [16,23] Inhibition of tumor production has been documented for xenograft models, and chemically induced tumors of the mouse skin and rat colon.[18, 19, 21]

药品 **Name**	剂量 **Dose**	药效 **Duration**	途径 **Route**	建议 **Recommendation**
布洛芬 Ibuprofen	40 mg/kg (Mouse) 20 mg/kg (rat)		PO (in water bottle)	Must be placed 24-48 hours in advance of surgical procedure to ensure therapeutic levels have been reached
Meloxicam	5mg/kg (mouse, rat)	Every 24 h	PO	Syringe without needle should be placed in the cheek of a manually restrained rodent

NARCOTICS (OPIOIDS)

Bind to mu, delta and kappa receptors to produce analgesia by blocking nociception and also affect the limbic system, which makes pain more tolerable. Opioids may be classified as agonists (morphine), agonist-antagonists (butorphanol) or partial agonists (buprenorphine) in their activity on these receptors. They are generally indicated for moderate to severe acute pain. Adverse effects have been observed when high doses of opioids are given to pain-free animals including gastrointestinal issues, bradycardia, hypotension, dizziness.[4,5,6,15] At clinical doses, respiratory depression and sedation are minimal with buprenorphine[6,14, 22] but elevation of both biliary tract and CSF (cerebral spinal fluid) pressure has been noted. [7] Potential impacts on

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fetuses should be considered as opioids do cross the placental barrier. [6, 10, 22]				
药品 Name	**剂量 Dose**	**药效 Duration**	**途径 Route**	**建议 Recommendation**
丁丙诺啡 Buprenorphine	0.1mg/kg	Every 8-12 h	SC	Mice: 0.1mL buprenorphine + 0.9 mL sterile saline to make a 0.03 mg/ml solution
	0.05mg/kg	Every 8-12 h	SC	Rat: 0.1mL buprenorphine + 0.9 mL sterile saline to make a 0.03 mg/ml solution

无法缓解的疼痛 Unrelieved Pain and Distress

无法缓解的疼痛与手术相关，可以通过对下丘脑垂体肾上腺轴（HPAA）、淋巴细胞增殖和自然杀手（NK）细胞活动的影响，对患者的免疫抑制做出贡献。这样的影响会混淆研究结果，也会影响动物的福利。除非 IACUC 已经批准了基于记录的对特定模型的干扰的止痛剂，否则必须使用止痛剂来减轻疼痛。在某些情况下，IACUC 可能需要执行一个试点研究确定止痛药的效果的具体模式如果没有发布信息的决心，未减轻的疼痛或痛苦也可以对数据收集有显著影响。Unrelieved pain/distress associated with surgery can contribute to immunosuppression of the patient through effects on the hypothalamic pituitary adrenal axis (HPAA), lymphocyte proliferation, and natural killer (NK) cell activity. 11 Such impacts can confound research results as well as impact the welfare of the animal. Unless the IACUC has approved withholding of analgesics based on documented interference with the specific model of interest, analgesics must be used to alleviate pain. In some cases, the IACUC may require a pilot study be performed to determine the effect of analgesics on the specific model if there is no published information on which to make the determination, keeping in mind that unrelieved pain or distress can also have a significant effect on data collection.

注意 PLEASE NOTE：研究人员和 IACUC 不仅需要考虑麻醉或止痛剂是否会影响研究数据，还需要考虑从伦理出发，即这项研究的潜在益处是否超过了无法缓解的疼痛或痛苦。Researchers and the IACUC need to consider not just the factual question of whether anesthesia or analgesics would invalidate the study, but also the ethical judgement whether the potential benefits of the study outweigh the unrelieved pain or distress.[2]

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