RAT: Analgesia and Anesthesia formulary

The appropriate use of pain medications (analgesics) and anesthetics is a critical aspect of the proper care and use of animals in research. Not only are they required by both the ethical conduct of research and regulatory agencies when an animal experiences more than momentary pain or discomfort, but minimization of pain and stress typically results in better, more reproducible results. (Resources to Aid in Recognition of Pain and Distress; Pain Relief in Animals)

The following is a listing of dosages for many of the more commonly employed analgesics and anesthetics, and is meant as a guide during protocol preparation. In all cases, animals may only be utilized with a currently IACUC approved protocol and any changes in the analgesics or anesthetics must be accompanied by an amendment to the protocol even if the medication is listed in this formulary.

The formulary is **not** meant to be an all-inclusive listing. If you would like to use a drug not included in this listing, please contact a DLAM veterinarian to discuss its use in your protocol.

Variability amongst models

The doses listed in the formulary were collected from the comparative medicine literature, but these articles typically evaluate rodent drug doses using the *most common* strains or stocks and *healthy* animals in the case of large animal trials. Moreover, it is well recognized there can be considerable variation in the effect of drugs across individuals, strains and stocks, as well as between sexes. Thus, it is critical to evaluate all animals, including strains or models that you have created, to determine if the doses and/or drugs chosen are appropriate in your study.

If your research focuses on a particular body system, it is also important to consider the effect of the drug on that system. We encourage you to work with the Division of Laboratory Animal Medicine (DLAM) veterinarians and/or review the literature for this information. There have been a considerable number of articles in the comparative medicine literature focusing on these considerations.

Selecting an appropriate analgesic or anesthetic

In most cases, the formulary includes information regarding the time of onset and duration of effect. In general, the opiates are shorter-acting than Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and can be effectively used at the time of the procedure to dampen the induction of the pain pathways. The pain and discomfort which occurs later is typically attributed to inflammation, therefore, NSAIDs are used in many post-operative regimens. When using multiple drugs, it is also critical to consider their potential interactions. For example, certain opiates can actually antagonize each other's actions, thus cancelling their beneficial effect.

Additional resources

Currently there are a number of excellent textbooks about laboratory animal anesthesia and pain management available online through the UNC Library system. A select few are as follows:

1) http://search.lib.unc.edu/search?R=UNCb6247400 Laboratory animal anaesthesia, Flecknell, P. A. Elsevier/Academic Press, Amsterdam, Boston, 2009.
2) http://search.lib.unc.edu/search?R=UNCb6554539 Handbook of laboratory animal science.Volume 1, Essential principles and practices, CRC Press, Boca Raton, FL, 2011.

Rat Analgesia

NOTE: There is considerable strain and individual animal variation. All rodents should be assessed for analgesic effect after analgesic administration. Administration of analgesics in food or water may lead to inadequate dosing due to lack of palatability, diurnal patterns of food consumption, pain induced anorexia, or reduction of drinking. Use of medicated water should be combined with other analgesic methods to ensure adequate pain control. The use of multiple classes of analgesics that act on different pain pathways (multimodal analgesia) is likely to enhance pain relief. Pre-emptive analgesia, blocking the induction phase of surgical pain, has been shown to be highly effective.

Drug	**Dose (mg/kg)**	**Route**	**Interval (hours)**	**Effect**	**Notes**
Opioids - *can be associated with pica (dose and strain related effect). Consider adverse effects - respiratory depression, GI stasis, excitement and/or sedation.*					
Buprenorphine	0.01 - 0.05 Note that higher doses may be used in a range of 0.01- 0.1 but that > 0.05 may be associated with pica in rats *Dosing for <u>Buprenorphine ER:</u> single subcutaneous injection of 0.10 mL per 200 gram rat (0.65 mg/kg body weight). <u>SR</u>: 1.0- 1.2 mg/kg	SC, IP, IV SC SC	6 - 8 (higher end of dosage range leads to longer effect) 48- 72 48-72	mild to moderate pain of increased duration	maximum analgesic effect reached 30 min post injection, beneficial effect on post-operative recovery * Buprenorphine SR (sustained release) is available for use in rodents. * Buprenorphine ER (extended Release) is also available–See dosing info in 2nd column. SR & ER formulations can also be associated with pica in rats.
Butorphanol	1.0 - 2.0	SC	1 - 2	mild pain of short duration	
Morphine	1.0 – 4.0 2.0 – 10 0.01 – 3.0	IV SC, IM SC*	2 – 3* (0.5 hr before, and 0.5 hr after and post-surgery is most effective)	Effective with in 15 min. For severe pain, re-dose every 2-3 hrs	Analgesia. Sedation and respiratory depression seen at higher dosages
Oxymorphone	0.2 - 0.5 0.03 mg/kg/hr 0.1	SC IV IV	4 CRI*	better than buprenorphine when given post operatively for visceral pain	*CRI= Continuous rate infusion
Tramadol	12.5	IP	4 - 12		does not cause sedation or skin lesions at this dosage range

NSAIDS - *adverse effects may include blood dyscrasias, interference with platelet function and the targeting of GI, hepatic and renal tissues following prolonged administration. Best not to administer to animals with pre-existing renal disease or fluid deficits. Otherwise these effects are rarely of significance when treating for 2-3 days. This class should be combined with opioids for surgery models.*

Drug	Dose (mg/kg)	Route	Interval (hours)	Effect	Notes
Acetaminophen	200	PO gavage -in water		mild pain, little anti-inflammatory action	Acclimatize to flavored water prior to treatment: **6.0 mg/ml** dose for adding to water bottle. Not an ideal choice for analgesic; non anti-inflammatory
Carprofen	1.0 - 5.0	SC, PO	12 - 24	effective for post-operative pain	most commonly used, wide safety margin
Ketoprofen	5.0 5.0 - 15 10 - 20	PO SC IP	12 - 24	moderate pain, co-administration with caffeine potentiates effect 2-3 times that of ketoprofen alone	most commonly used, wide safety margin
Meloxicam	1.0 1.0 - 4.0	PO SC, IP	12 - 24	post-operative pain	most commonly used, wide safety margin
Aspirin	100 20 110 - 120	PO SC IP	12	mild pain, least effective for visceral pain, most effective for musculoskeletal	can cause fetal abnormalities, avoid in pregnant animals
Ibuprofen	40 - 200 200	PO SC	8 - 12	co-administration with caffeine has similar analgesic profile to that of morphine	--- addition of opioids SC potentiates effect, hydrocodone (2.3 mg/kg), methadone (1.7 mg/kg), oxycodone (0.5 mg/kg)
Celecoxib	10 - 20	PO	12	post-operative and chronic pain	ineffective against bone cancer and thermal pain, pre-emptive administration is highly effective

Local Anesthetics - use as an adjuvant to primary anesthetic agents

Drug	Dose (mg/kg)	Route	Interval (hours)	Effect	Notes
Lidocaine	0.67 - 1.3 mg/kg/hr 2.0 - 7.0	SC CRI* -- infiltration	fast onset, moderate duration of action	most useful for local or regional, can be applied to mucous membranes on cornea	do not use epinephrine formulation, (0.05 - 0.2 ml total volume for 200 - 250g rat), *CRI = Continuous rate infusion

Bupivicaine	0.125% or 0.25%?	SC- local infiltration	4 - 7 slower onset, longer duration	most useful for local or regional, 4 x potent as %/vol.	
Antidepressants- *first line drugs for neuropathic pain and used widely for chronic pain. These drugs have analgesic activity independent of their mood-altering properties. Neuropathic pain involves pain in a neuroanatomical area or a history or confirmation of relevant disease or lesion in the nervous system.*					
Drug	**Dose (mg/kg)**	**Route**	**Interval (hours)**	**Effect**	**Notes**
Amitriptyline	1.0 - 10 0.5 - 2.0	SC, IP IV	3 - 12	neuropathic pain	studied up to 2 weeks with no tolerance or overt adverse effects
Imipramine	10	SC, IP	12 - 24	neuropathic pain	studied up to 2 weeks with no tolerance or overt adverse effects
Gabapentin	10 - 100 10 - 30	PO IP	6 - 8	neuropathic pain	

Rat Anesthesia				
NOTE: There is considerable variation in the length and depth of sedation and anesthesia related to strain, sex, size and health status. All rodents should be assessed for anesthetic effect after administration.				
Drug	**Dose (mg/kg)**	**Route**	**Effect**	**Notes**
Anesthesia - Preferred injectables and their combinations				
Dexmedetomidine	15 - 50 ug/kg	SC (IP)	light to heavy sedation, mild to moderate analgesia	IP injections may have less effect due to possible hepatic first pass effect, reverse with atipamizole 0.1 - 1.0 mg/kg IM or IP
Ketamine / Diazepam	40 /20 45 - 60 / 5.0 - 10	IP	45 - 60 minutes of anesthesia	can cause hypothermia
Ketamine/ Dexmedetomidine	50 - 75 / 1.0 - 10 60 / 0.4 75 / 1 75 / 0.5	IP	surgical anesthesia (20 - 30 min)	can cause hypothermia, reverse with atipamizole 0.1 - 1.0 mg/kg IM or IP
Ketamine/ Xylazine	75 - 100 / 5.0 - 10	IP, IM	surgical anesthesia (20 - 30 min)	IM (not preferred route of administration), can cause hypothermia, ocular lesions tissue reactions and discomfort, safe for pregnancy
Ketamine/ Xylazine/ Acepromazine	40/8.0/4.0 40 -5 0 / 2.5 / 0.75	IP, IM		IM (not preferred route of administration), can cause hypothermia, ocular lesions tissue reactions and discomfort, safe for pregnancy
Propofol	7.5 - 10	IV	induction, surgical anesthesia (~5 min unless CRI*)	*CRI= Continuous rate infusion
Tiletamine/ Zolaepam	20 - 40	IP	light anesthesia	
Tribromoethanol / Dexmedetomidine	150 /0.25	IP	reverse with atipamizole	consider alternative injectable anesthetics for multiple uses

Tribromoethanol	300 (0.25% sol)	IP	rapid induction, loss of reflex and muscle relaxation	can cause illness (abdominal muscle necrosis, peritoneal inflammation, visceral adhesions) and death several days after dosing, ileus and impaired reproduction have also been noted, refer to IACUC SOP for proper use
General Anesthesia - *Ideally for long duration or terminal anesthesia- Refer to Environmental, Health and Safety policy for proper use and handling of these agents. Non-preferred anesthetics due to increased risk of negative side effects. Special purpose benefits are italicized.*				
Drug	**Dose (mg/kg)**	**Route**	**Effect**	**Notes**
Urethane	1000	IP	for procedures of exceptionally long duration	can be combined with alpha chloralose, *long duration with preservation of autonomic reflexes*
Thiobarbitol (Inactin)	80- 100	IP	stable anesthesia for 3 hours, minimal effect on cardiovascular tone and renal output	can be combined with ketamine for longer duration of action, additional doses may be needed for prolonged procedures, *most useful for very long anesthetic procedures.*
Alpha Chlorase	31 - 65	IP	hypnotic anesthetic with little analgesic effect	*primarily physiologic experiments for maintenance of respiratory and cardiac reflexes*, less useful for invasive surgery, can cause ileus
Pentobarbital (Nembutal)	30 - 60	IP	60 - 120 min of anesthesia, minimal analgesic effect, quality of anesthesia considered poor	minimal to no impact on glucose levels, cardiovascular and respiratory effects have been noted, males clear drug more rapidly than females, *recommended for acute/terminal procedures, euthanize and harvest, trans-cardial perfusions*
Inhalants - *refer to Environmental, Health and Safety policy for proper use and handling of these agents.*				
Drug	**Dose (mg/kg)**	**Route**	**Effect**	**Notes**
Isoflurane / Morphine	2% / 5	Inhaled / SC	induction and maintenance	
Sevoflurane	2.0 - 2.4%	Inhaled	maintenance	
Isoflurane	5% 0.25% - 2.5%	Inhaled Inhaled	induction maintenance	Requires inhalational anesthetic training; Isoflurane Drop Method