Curtin University Standard Operating Procedure

USE OF ANALGESIA IN RODENTS

Number: TEC 10
Version: 1.2
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Aims / Objectives: To provide current recommendations for analgesia for rodents used at Curtin University.

Definitions:
Analgesia: means "without pain"

Analgesics: drugs which are used to decrease or prevent the perception of pain.

Pain: can result in significant and undesirable physiological, biochemical, and behavioural changes in the animal, resulting in false results from research projects

Pain Management Protocol: involves a plan to anticipate, prevent and alleviate pain for each individual animal. It must be a safe, effective and humane protocol suitable for the scientific project being carried out.

Opioid Drugs: these are drugs which act on the opioid centre in the brain to alleviate the pain experienced by an animal. Examples include morphine, pethidine, butorphanol, buprenorphine and tramadol.
Advantages include a good level of pain relief, and its use may lower the dosage of anaesthetic required.
Disadvantages include respiratory depression and they are controlled substances which require a licence to dispense.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs): These are drugs which acts to both reduce inflammation in the body, and to stop the transmission of pain along the pain pathways.

Advantages: They often act up to 24 hours, and may be used concurrently with anaesthetics, with opioid analgesics, and with local anaesthetic/analgesics. Injectable NSAIDs are useful for accurate dosaging and administration to small rodents. Disadvantages: They need to be used with caution due to their effects on the kidney and liver, especially if used over a long period or there are predisposing problems with the kidneys or liver. They can also decrease clotting ability, which is of possible concern following surgery. NSAIDs can cause gastric upsets and ulceration, especially with long term use. It is generally recommended to limit their use in small animals to 3-4 days duration.

Local Anaesthesia: Can be used to provide pain relief during or after a procedure by blocking all the pain sensation from a particular area. Lignocaine can be used for short term relief, as can Lidocaine cream (EMLA), which can be used topically on shaved, intact skin prior to venepuncture, though it requires 30-60 minutes or more of contact with skin to reach full effect.
Methods of Administration are:
PO – Per os – oral administration. Mice and Rats may need to be trained to accept drugs in an oral form- such as through the use of jelly.
IV- Intravenous administration
IM – Intramuscular administration
SC – Subcutaneous administration

Procedures:
It is not the role of the AEC or of the Animal Facility staff to decide on the level of impact the analgesic drugs may or may not have on experimental data. However analgesia is mandatory in all animals undergoing any procedure which may lead to pain, unless otherwise approved by the AEC.

The drugs available in the animal facility are listed below at their recommended dosages for mice and rats. Each individual project however should be discussed with the animal welfare officer and / or the facility manager to ensure the correct pain relief management has been instigated for those particular animals, and approved in the AEC application process. The dosage, the route, the frequency, and the timing of the pain relief will all vary with each project and the likely degree of pain for the individual procedure.

Drug	Rat	Mouse
Buprenorphine (an opioid drug) (NHMRC, 2008)	0.01-0.05mg/kg SC, IV 8-12 hourly 0.1-0.25mg/kg PO 8-12 hourly	0.05-0.1mg/kg SC 8-12 hourly
Meloxicam (a NSAID) (NHMRC, 2008)	1mg/kg SC,PO 24 hourly	1-2mg/kg SC 24 hourly

1) See the following page for specific SOP for the use of the above mentioned analgesics.

2) Other drugs available, but not held in stock at the facility, can be found in NHMRC Guidelines to promote the wellbeing of animals used for scientific purposes (http://www.nhmrc.gov.au/guidelines/publications/ea18).

Examples of surgeries and the level of pain caused in rodents (1):

Minimal to Mild Pain	Moderate Pain	Moderate to Severe Pain
Percutaneous Vascular catheter implantation	Minor Laparotomy Incision	Major laparotomy/organ incision
Ear Notching	Thyroidectomy	Thoracotomy
Superficial Tumour Implantation	Orchidectomy	Heterotopic organ transplantation
Ocular procedures	C-section Embryo transfer	Vertebral procedures
Multiple injections	Vascular access port	Burn procedures
	Indwelling vascular cannulae	Trauma models
	Intracerebral implantation	Orthopaedic procedures
	Osmotic pump implant	Caecal ligation and puncture

Analgesics required for alleviating various levels of pain in rodents (1):

Minimal to Mild Pain	Mild to Moderate Pain	Moderate to Severe Pain
Meloxicam or Ketoprofen* **OR**	Buprenorphine **OR**	Buprenorphine or Morphine* **AND**
Buprenorphine	Meloxicam or Ketoprofen*	Meloxicam or Ketoprofen*

*These drugs can be ordered in if required.

References:

1) The University of British Columbia website: http://www.animalcare.ubc.ca/anesthesia_analgesia.html

2) NHMRC 2008 Guidelines to Promote the Wellbeing of Animals used for Scientific Purposes http://www.nhmrc.gov.au/guidelines/publications/ea18

3) Roughan J.V., Flecknell, P.A. (2002) Buprenorphine: a reappraisal of its antinociceptive effects and therapeutic use in alleviating post-operative pain in animals. Laboratory Animals 36 (322-343)

4) Stokes, E L; Flecknell P A; Richardson C A (2009) Reported analgesic and anaesthetic administration to rodents undergoing experimental surgical Lab Anim 2009 43: 149

http://lan.sagepub.com/content/43/2/149

See also SOP TEC 15 Calculating Drug Dosages for Animals

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Standard Operating Procedure for Meloxicam Usage

Purpose: To provide pain relief and / or reduce inflammation in cases of mild to moderate pain in mice and rats, such as that caused by minor surgical procedures, fight wounds, eye trauma etc. In cases of severe pain, NSAIDs should be used in conjunction with opioids and other forms of pain relief.
Meloxicam (Metacam®) is a NSAID which is commonly used in rats and mice and provides 24 hours of pain relief.

Materials:

1. Meloxicam: comes in 2 forms- an oral liquid (1.5mg/ml) or an injectable form (5mg/ml). We stock Meloxicam as an injectable form; however we can order in the oral form if required.

2. Needles (25-27G) and Syringes (these need to be small enough to accurately deliver small volumes such as disposable insulin syringes or sterile Hamilton syringes.

3. Sterile saline or PBS for injections- to use to dilute the liquid.

Procedures:
Dilution: Dilute the injectable Meloxicam® 1ml into 9ml water for injection giving a concentration of 0.5mg/ml. Discard this diluted solution if not used within a month's time.

1. Weigh the mouse or rat
2. Draw up the required amount of Meloxicam

Rat Dose: 1mg/kg SC or PO ONCE daily for up to 3 days

Rat Weight	Injectable (Diluted to 0.5mg/ml)	Oral Solution (1.5mg/ml)
250g	0.5ml	0.16ml
300g	0.6ml	0.20ml
350g	0.7ml	0.23ml
400g	0.8ml	0.26ml
450g	0.9ml	0.30ml

Mice dose: 1-2 mg/kg SC ONCE daily for up to 3 days

Mouse Weight	Injectable (Diluted to 0.5mg/ml)
20g	0.04-0.08ml
25g	0.05-0.1ml
30g	0.06ml-0.12ml
35g	0.07ml-0.14ml
40g	0.08-0.16ml

3. For oral administration: while gently restraining the rat, administer the suspension gently and directly into the mouth one drop at a time until the animal ingests the fluid. Do not force the entire dose at once as the animal may inhale the liquid which can lead to death.

4. If it is to be injected, administer subcutaneously in the scruff (loose skin on dorsal neck) using a 25g or 27g needle.

5. Do not treat for more than 3 days.

6. Discard the needle and syringe safely into the appropriate sharps container found in the facility.

Meloxicam can be used pre-operatively or post operatively and in combination with an opioid analgesic for controlling moderate to severe pain. Side effects may include a decrease in appetite. Use with caution in animals with pre-existing renal, cardiovascular, or liver disease.

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Standard Operating Procedure for Buprenorphine (Temgesic®) Usage

Purpose: To provide pain relief in mice and rats either pre or post operatively using an opioid drug which provides moderate to high pain relief. It can be combined with other drugs, such as NSAIDs, to increase the level of pain relief.
Buprenorphine acts for 10-12 hours, and acts on the opioid receptors in the brain.
It is an S8 drug and is strictly regulated. It must be recorded after each use and the facility is accountable for every ml dispensed to animals.

Materials:

1. Temgesic® comes in 1ml vials of a concentration of 0.3mg/ml for injecting or as tablets 0.2mg/tablet for oral administration

2. Needles (25G or 27G) and insulin syringes

3. Sterile saline to dilute the concentration

Methods:

1) Weigh the animal

2) Calculate the dose required.

3) Dilute the Temgesic® 1:10 by putting 0.1ml Temgesic® into 0.9ml saline to make a concentration of 0.03mg/ml.

Mouse: 0.05-0.1mg/kg SC (NHMRC, 2008)

Mouse Weight	Temgesic® SC (Diluted to 0.03mg/ml)
20g	0.03-0.06ml
25g	0.04-0.08ml
30g	0.05-0.1ml
35g	0.06-0.12ml
40g	0.07-0.14ml

Rat: 0.01 -0.05mg/kg SC,IV or 0.1-0.25mg/kg PO (NHMRC, 2008)

Rat Weight	Temgesic® SC IV (Diluted to 0.03mg/ml) 0.01-0.05mg/kg	Temgesic® (undiluted 0.3mg/ml) PO 0.1-0.25mg/kg
250g	0.08-0.4ml	0.08-0.21ml
300g	0.1ml- 0.5ml	0.1-0.25ml
350g	0.12-0.58ml	0.11- 0.29ml
400g	0.14-0.67ml	0.13-0.33ml
450g	0.16-0.75ml	0.15-0.37ml

4) Inject the animal subcutaneously by scruffing the mouse or rat around the dorsal neck and injecting under the skin.

5) In rats, the buprenorphine can be given orally into the mouth. This should be done by gently holding the rat, and slowly dropping into the mouth until the rat swallows the medication. It should not be forced into the mouth as may be inhaled and can cause fatal aspiration pneumonia. Another method of oral administration of the buprenorphine in rats is to use jelly.

6) For any unused portion of the drugs, please return to Facility Staff and inform the facility staff of dosages used, and fill out the register of drugs at the office of the facility.

7) Discard the needle and syringe safely into the appropriate sharps container found in the facility.

Possible Side Effects:
In rats, it has been seen that in some animals, the use of buprenorphine may induce pica (eating their own faeces) in some animals so upon waking post operatively and whilst the buprenorphine is being administered, animals should be kept on alternative bedding material to prevent ingestion of the bedding which may lead to potentially life threatening obstructions.

Also in rats, buprenorphine given prior to a xylazine/ketamine anaesthetic has been shown to have adverse effects so it is not recommended to use these drugs in combination.

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