McGill

STANDARD OPERATING PROCEDURE #103

NON-HUMAN PRIMATE ANALGESIA

1. PURPOSE

The intent of this Standard Operating Procedure (SOP) is to describe methods of assessing pain in non-human primates and mitigating pain by administration of analgesic medications.

2. RESPONSIBILITY

Principal investigators (PI) and their staff, veterinary and animal care staff, and any personnel who will monitor animals undergoing potentially painful procedures.

3. GENERAL CONSIDERATIONS

3.1. A procedure which would be expected to be painful if it were done on human must be considered painful to the animal.

3.2. When there is a question of whether or not a procedure is painful, the animal should receive the benefit of analgesia.

3.3. Analgesia should be provided at an appropriate dose and frequency to control pain.

3.4. Any deviation from this procedure must be justified by the investigator and approved by the appropriate Facility Animal Care Committee (FACC).

4. PAIN RECOGNITION AND ASSESSMENT

4.1. Adapt the frequency of observation to the protocol (minimum once a day).

4.2. Start by observing the animal from a distance so the animal's behavior is not altered by the presence of the observer. Then proceed to observe the animal more closely.

4.3. Look for any changes in the behavior. Report animals which appear to be in pain to the veterinary care staff.

Note: The most reliable signs of pain and distress are the changes in behavior. This implies a good knowledge of species and individual normal behavior by the observer.

4.4. Wild animals will usually hide any signs of pain.

5. ANALGESIA PLAN

5.1. If possible, provide analgesia before the painful stimulus, as it is more effective in preventing pain (e.g. give analgesic before surgery).

5.2. Try to use a combination of analgesics, which is often more effective than using a single agent.
For example, administer a combination of buprenorphine, carprofen, and local infiltration of a local analgesic.

5.3. For surgical procedures, extend analgesia from pre-op to 72 hours post-op, unless specified otherwise in the Animal Use Protocol (AUP) and approved by the FACC.

6. LOCAL ANALGESIA

6.1. Infiltrate or apply local analgesic to areas where a painful stimulus may be induced. Repeat application of local agent at specified intervals to maintain analgesia. In some cases a sedative is recommended when using local analgesia.

Analgesic	Dose	Duration	Note
Lidocaine	< 2 mg/kg	30–60 min.	Use lidocaine HCl 2% (20mg/ml) injectable solution. Because this drug is acidic, it is recommended to dilute it 3:1 with sodium bicarbonate injectable solution (at 5 or 8.4%). Dilution with sodium bicarbonate is not necessary if lidocaine is to be administered to an anesthetized animal. Dilution must be prepared immediately before use and should not be stored. Diluted solution is as effective but induction of analgesia is slightly prolonged.
Bupivacaine	< 2 mg/kg	3–4 hrs.	Use bupivacaine HCl 0.50% (5mg/ml) injectable solution. Same comment as for lidocaine.
* Lidocaine-bupivacaine mixture	< 2 mg/kg	30 min. to 4 hrs.	Same comment as for lidocaine. Combining both drugs allows for rapid induction and prolonged effect. Discard mixture after 3 months.
EMLA cream	Thick spread	30–60 min.	Shave fur and apply a thick layer of cream ideally 10 minutes before the painful procedure

*most commonly used

7. GENERAL ANALGESIA

Non-human primates

Analgesic	Dose	Route	Frequency	Note
Acetaminophen	15 mg/kg	PO	4-6 hrs.	For mild pain.
*Buprenorphine	0.005–0.02 mg/kg	IM (preferred) IV, SC	6-8 hrs (low dose) 8–12 hrs (high dose)	Controlled drug.
Buprenorphine Slow Release (SR)	0.2 mg/kg	SC	72-120 hrs	Buprenorphine SR (3mg/ml) is a sustained release buprenorphine product that has been developed to provide up to 120 hours of analgesia in NHPs. See administration instructions in section 7.1. Controlled drug.
*Carprofen	2-4 mg/kg	SC, IM	12-24 hrs.	4mg/kg first dose, then 2mg/kg.

Analgesic	Dose	Route	Frequency	Note
Fentanyl	Patch 25µg (3-7kg BW)		Every 3 days, starting 24h prior to surgery	Protect patch under a jacket. Controlled drug.
Morphine-Lidocaine-Ketamine Combination	2 ml/kg/hr	IV	Constant rate infusion	To a 500ml bag of fluids, add morphine 60mg, lidocaine 750mg and ketamine 150mg. Controlled drugs.
Ketamine	0.1-1.0 mg/kg	SC, IM, IV	-	After initial bolus, constant rate infusion of 0.1-0.3 mg/kg/hr. Controlled drug.
*Ketoprofen	1–2 mg/kg	SC, IM, IV	12–24 hrs.	2mg/kg first day, then 1mg/kg.
*Meloxicam	0.1-0.2 mg/kg	SC, PO	24 hrs.	0.2mg/kg first day, then 0.1mg/kg.

*most commonly used

7.1. Administration instructions for buprenorphine slow release (SR):

7.1.1. Avoid contact with the skin to prevent the development of injection site reactions.

7.1.2. For use in NHPs: draw up the buprenorphine SR with an 18G needle and change to a 23g needle prior to administration.

7.1.3. Administer slowly and finish injecting before the needle is pulled out through skin.

7.1.4. Pinch the injection site for approximately 10 seconds after removing the needle.

7.1.5. Do not combine in the same syringe the buprenorphine SR with any other drugs in the same syringe and do not attempt to dilute the formulation.

7.2. Administration of non-steroidal anti-inflammatory drugs (NSAIDs):

7.2.1. NSAIDs include carprofen, ketoprofen and meloxicam.

7.2.2. Ensure good water intake and monitor hydration status during the treatment period.

7.2.3. Suspend water restriction prior to administration of NSAIDs.

7.2.4. To minimize chances for adverse drug interactions, a washout period of 5-7 days is recommended before switching between NSAIDs.

8. REFERENCES

8.1. Nunamaker, EA, Halliday LC, Moody DE, Fang WB, Lindelblad M, Fortman JD. (2013). Pharmacokinetics of 2 Formulations of Buprenorphine in Macaques (*Macaca mulatta* and *Macaca fascicularis*). *JAALAS* **52**:48-56. http://www.ncbi.nlm.nih.gov/pubmed/23562033

SOP REVISION HISTORY

DATE	PREVIOUS VERSION	NEW VERSION
2015.04.22	6.1 (NO TEXT)	6.1 **Use lidocaine HCl 2% (20mg/ml) injectable solution.**
2015.04.22	6.1 (NO TEXT)	6.1 **Use bupivacaine HCl 0.50% (5mg/ml) injectable solution.**
2015.04.22	6.1 (NO TEXT)	6.1 Lidocaine-bupivacaine mixture: **Discard mixture after 3 months.**
2016.02.01	7. Buprenorphine route of administration: SC	7. Buprenorphine route of administration: **IM**, SC
2016.02.01	7. Meloxicam route of administration: SC	7. Meloxicam route of administration: SC, **PO**
2016.02.01	7. Buprenorphine dose: 0.005–0.01 mg/kg	7. Buprenorphine dose: 0.005–~~0.01~~ **0.02** mg/kg
2016.02.01	7. (NO TEXT)	**Buprenorphine Slow Release (SR)** **Dose: 0.2 mg/kg** **Route of administration: SC** **Frequency: 72-120 hrs** **Note: Buprenorphine SR (3mg/ml) is a sustained release buprenorphine product that has been developed to provide up to 120 hours of analgesia in NHPs. See administration instructions in section 7.1.** **Controlled drug.**
2016.02.01	7.1 (NO TEXT)	**7.1. Administration instructions for buprenorphine slow release (SR):** **7.1.1. Avoid contact with the skin to prevent the development of injection site reactions.** **7.1.2. For use in NHPs: draw up the buprenorphine SR with an 18G needle and change to a 23g needle prior to administration.** **7.1.3. Administer slowly and finish injecting before the needle is pulled out through skin.** **7.1.4. Pinch the injection site for approximately 10 seconds after removing the needle.** **7.1.5. Do not combine in the same syringe the buprenorphine SR with any other drugs and do not attempt to dilute the formulation.**
2016.09.02	7. (NO TEXT)	7. Carprofen, ketoprofen and meloxicam: **Ensure good water intake and monitor hydration status.** **Suspend water restriction prior to administration.**
2016.09.02	Buprenorphine route of administration: IM, SC	Buprenorphine route of administration: IM **(preferred)** **IV,** SC
2016.09.02	5.2 For example, administer a combination of buprenorphine, ketoprofen, and local infiltration of lidocaine	5.2 For example, administer a combination of buprenorphine, ~~ketoprofen~~ **carprofen**, and local infiltration of ~~lidocaine~~ **a local analgesic.**
2017.01.27	7.2 (NO TEXT)	**7.2. Administration of non-steroidal anti-inflammatory drugs (NSAIDs):** **7.2.1. NSAIDs include carprofen, ketoprofen and meloxicam.** **7.2.2. Ensure good water intake and monitor hydration status during the treatment period.** **7.2.3. Suspend water restriction prior to administration of NSAIDs.** **7.2.4. To minimize chances for adverse drug interactions, a washout period of 5-7 days is recommended before switching between NSAIDs.**
2018.10.12	7.1.5. Do not combine in the same syringe the buprenorphine SR with any other drugs and do not attempt to dilute the formulation.	7.1.5. Do not combine in the same syringe the buprenorphine SR with any other drugs **in the same syringe** and do not attempt to dilute the formulation.