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, veterinarians, veterinary and animal care staff.

3. GENERAL CONSIDERATIONS

3.1. A procedure which would be expected to be painful if it were done on humans 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 Animal Care Committee (ACC).

4. PAIN RECOGNITION AND ASSESSMENT

4.1. Adapt the frequency of observation to the invasiveness of the procedure (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.

4.4. Wild animals will usually hide any signs of pain. Common clinical signs indicative of pain or distress include:

- 4.4.1. Avoidance
- 4.4.2. Vocalization
- 4.4.3. Eyebrow movements
- 4.4.4. Escape and aggressiveness
- 4.4.5. Spontaneous activities are reduced; the animal is isolated from the social group
- 4.4.6. Apathy, anxiety, plaintive
- 4.4.7. Altered gait
- 4.4.8. Nibbling, licking, scratching, rubbing
- 4.4.9. Eyes are semi-closed
- 4.4.10. Head shaking (ear pain)
- 4.4.11. Reduced appetite and subsequent weight loss

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.

4.5. Consult ethograms and grimace scales adapted to the primate species as a means of assessing pain levels using observation of behavior, facial expressions, and posture.

5. ANALGESIA PLAN

5.1. Provide analgesia before the painful stimulus, at least 30 to 60 minutes before the procedure, as it is more effective in preventing pain.

5.2. Use a combination of analgesics, which is often more effective than using a single agent. For example, a combination of opioid, non-steroidal anti-inflammatory drug (NSAID), and 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 ACC.

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	Route	Duration	Note
Lidocaine	2 – 4 mg/kg Not to exceed 5 mg/kg	SC, Infiltration of surgical wounds	30–60 min.	Use lidocaine HCl 2% (20mg/ml) injectable solution. When necessary, lidocaine may be diluted in 0.9% sodium chloride (isotonic saline solution).
Bupivacaine	1 - 2 mg/kg	SC, Infiltration of surgical wounds	3–4 hrs.	Use bupivacaine HCl 0.50% (5mg/ml) injectable solution. When necessary, bupivacaine may be diluted in 0.9% sodium chloride (isotonic saline solution).
EMLA cream	Thick spread	Topical	30–60 min.	Shave fur and apply a thick layer of cream at least 10 minutes before the painful procedure.

7. GENERAL ANALGESIA

Macaques

Analgesic	Dose	Route	Frequency	Note
*Buprenorphine	0.005–0.03 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	48-72 hrs	Buprenorphine SR is a sustained release buprenorphine product that has been developed to provide up to 72 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.
Fentanyl	0.5-0.15 µg/kg (bolus) 7-20 µg/kg/hr (constant rate infusion)	IM IV	Bolus Constant rate infusion	For moderate to severe pain. Controlled drug.
Ketoprofen	1–2 mg/kg	SC, IM, IV	12–24 hrs.	2mg/kg first day, then 1mg/kg.

Macaques

Analgesic	Dose	Route	Frequency	Note
*Meloxicam	0.1-0.2 mg/kg	SC, PO	24 hrs.	0.2mg/kg first day, then 0.1mg/kg.
Meloxicam Slow Release (SR)	0.6 mg/kg	SC	48-72 hrs	Meloxicam SR (2mg/ml) is a sustained release meloxicam product that has been developed to provide up to 72 hours of analgesia in NHPs. See administration instructions in section 7.2.
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.

*most commonly used

Marmosets

Analgesic	Dose	Route	Frequency	Note
Carprofen	2-4 mg/kg	SC, PO	12-24 hrs.	4mg/kg first dose, then 2mg/kg.
Buprenorphine	0.005 – 0.02 mg/kg	IM, SC	6-8 hrs (low dose) 8–12 hrs (high dose)	Controlled drug.
Buprenorphine Slow Release (SR)	0.1-0.2 mg/kg	SC	48-72 hrs	Buprenorphine SR is a sustained release buprenorphine product that has been developed to provide up to 72 hours of analgesia in NHPs. See administration instructions in section 7.1. Controlled drug.
Meloxicam	0.1-0.2 mg/kg	SC, PO	24 hrs.	0.2mg/kg first day, then 0.1mg/kg.
Acetaminophen	6 mg/kg	PO	12-24 hrs	

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

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

7.1.4. Do not combine 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

8.2. Mackiewicz AL, Salyards GW, Knych HK, Hill AE, Christe KL. Pharmacokinetics of a Long-lasting, Highly Concentrated Buprenorphine Solution after Subcutaneous Administration in Rhesus Macaques (*Macaca mulatta*). *J Am Assoc Lab Anim Sci*. 2019;58(4):501–509. doi:10.30802/AALAS-JAALAS-18-000115.

8.3. DiVincenti L Jr. Analgesic use in nonhuman primates undergoing neurosurgical procedures. J Am Assoc Lab Anim Sci. 2013 Jan;52(1):10-6. PMID: 23562027; PMCID: PMC3548195.

8.4. Radulovic LL, Türck D, von Hodenberg A, Vollmer KO, McNally WP, DeHart PD, Hanson BJ, Bockbrader HN, Chang T. Disposition of gabapentin (neurontin) in mice, rats, dogs, and monkeys. Drug Metab Dispos. 1995 Apr;23(4):441-8. PMID: 7600909.

8.5. Sabrina R. Bourgeois, Maribel Vazquez & Kathleen Brasky (2007) Combination Therapy Reduces Self-injurious Behavior in a Chimpanzee (Pan Troglodytes Troglodytes): A Case Report, Journal of Applied Animal Welfare Science, 10:2, 123-140, DOI: 10.1080/10888700701313454.

8.6. Fabian, N. J., Moody, D. E., Averin, O., Fang, W. B., Jamiel, M., Fox, J. G., Burns, M. A., & Haupt, J. L. (2021). Pharmacokinetics of Single-Dose Intramuscular and Subcutaneous Injections of Buprenorphine in Common Marmosets (Callithrix jacchus). Journal of the American Association for Laboratory Animal Science : JAALAS, 60(5), 568–575. https://doi.org/10.30802/AALAS-JAALAS-20-000151

8.7. Paterson, E.A., O'Malley, C.I., Moody, C. et al. Development and validation of a cynomolgus macaque grimace scale for acute pain assessment. Sci Rep 13, 3209 (2023). https://doi.org/10.1038/s41598-023-30380-x

8.8. Carpenter J.W., Harms C. Carpenter's Exotic Animal Formulary, 6th Edition, September 2022.

8.9. Gadsden, J., Hadzic, A., Gandhi, K., Shariat, A., Xu, D., Maliakal, T., & Patel, V. (2011). The effect of mixing 1.5% mepivacaine and 0.5% bupivacaine on duration of analgesia and latency of block onset in ultrasound-guided interscalene block. Anesthesia and analgesia, 112(2), 471–476. https://doi.org/10.1213/ANE.0b013e3182042f7f

8.10. Cuvillon, P., Nouvellon, E., Ripart, J., Boyer, J. C., Dehour, L., Mahamat, A., L'hermite, J., Boisson, C., Vialles, N., Lefrant, J. Y., & de La Coussaye, J. E. (2009). A comparison of the pharmacodynamics and pharmacokinetics of bupivacaine, ropivacaine (with epinephrine) and their equal volume mixtures with lidocaine used for femoral and sciatic nerve blocks: a double-blind randomized study. Anesthesia and analgesia, 108(2), 641–649. https://doi.org/10.1213/ane.0b013e31819237f8

8.11. Onuma, K., Watanabe, M., & Sasaki, N. (2024). The grimace scale: a useful tool for assessing pain in laboratory animals. Experimental animals, 73(3), 234–245. https://doi.org/10.1538/expanim.24-0010

8.12. Goodroe, A., Fitz, C., & Bakker, J. (2020). Current Topics in Marmoset Anesthesia and Analgesia. ILAR journal, 61(2-3), 218–229. https://doi.org/10.1093/ilar/ilab001

8.13. Canadian Council on Animal Care. (2025). CCAC guidelines: Scientific procedures (Part B – Analgesia, anesthesia, and surgery).

SOP REVISION HISTORY

DATE	NEW VERSION
2025.01.21	4.5. ~~Use the Cynomolgus Macaque Grimace Scale (Paterson et al., 2023)~~ **Consult ethograms and** grimace scales **adapted to the primate species** ~~are one~~ **as a** means of assessing ~~the occurrence of acute~~ pain ~~using action units such as~~ **levels using observation of behavior,** facial expressions, and posture.
2025.01.21	5.1. **Provide** analgesia ~~should be provided~~ before the painful stimulus, **at least 30 to 60 minutes before the procedure,** as it is more effective in preventing pain ~~(e.g. give analgesic before surgery)~~.
2025.01.21	~~Lidocaine – bupivacaine mixture~~ ~~Dose: < 2 mg/kg~~ ~~Route of administration: SC, Infiltration of surgical wounds~~ ~~Duration: 30min. to 4 hrs.~~ ~~Note: Same comment as for lidocaine. Combining both drugs allows for rapid induction and prolonged effect. Use a 1:1 mixture of lidocaine HCl 2% (20mg/ml) injectable solution and bupivacaine HCl 0.50% (5mg/ml) injectable solution. Discard mixture after 3 months.~~
2025.01.21	EMLA cream Dose: Thick spread Route of administration: Topical Duration: 30–60 min. Note: Shave fur and apply a thick layer of cream ~~ideally~~ **at least** 10 minutes before the painful procedure. ~~Apply only to intact skin.~~
2025.01.21	~~7.1.2. Use a 23 G needle to draw up and administer the buprenorphine SR.~~

2025.01.21	**8.9. Gadsden, J., Hadzic, A., Gandhi, K., Shariat, A., Xu, D., Maliakal, T., & Patel, V. (2011). The effect of mixing 1.5% mepivacaine and 0.5% bupivacaine on duration of analgesia and latency of block onset in ultrasound-guided interscalene block. Anesthesia and analgesia, 112(2), 471–476. https://doi.org/10.1213/ANE.0b013e3182042f7f**
2025.01.21	**8.10. Cuvillon, P., Nouvellon, E., Ripart, J., Boyer, J. C., Dehour, L., Mahamat, A., L'hermite, J., Boisson, C., Vialles, N., Lefrant, J. Y., & de La Coussaye, J. E. (2009). A comparison of the pharmacodynamics and pharmacokinetics of bupivacaine, ropivacaine (with epinephrine) and their equal volume mixtures with lidocaine used for femoral and sciatic nerve blocks: a double-blind randomized study. Anesthesia and analgesia, 108(2), 641–649. https://doi.org/10.1213/ane.0b013e31819237f8**
2025.01.21	**8.11. Onuma, K., Watanabe, M., & Sasaki, N. (2024). The grimace scale: a useful tool for assessing pain in laboratory animals. Experimental animals, 73(3), 234–245. https://doi.org/10.1538/expanim.24-0010.**
2025.03.25	Lidocaine Dose: ~~<2~~ **2 - 4** mg/kg. **Not to exceed 5 mg/kg** Route of administration: SC, Infiltration of surgical wounds Duration: 30 - 60 min. Note: 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 must be prepared immediately before use and should not be stored. Diluted solution is as effective but induction of analgesia is slightly prolonged. *Dilution with sodium bicarbonate is not necessary if lidocaine is to be administered to an anesthetized animal.~~ **When necessary, lidocaine may be diluted in 0.9% sodium chloride (isotonic saline solution).**
2025.03.25	Bupivacaine (marmosets) Dose: ~~<2~~ **1 - 2** mg/kg Route of administration: SC, Infiltration of surgical wounds Duration: 3 - 4 hrs. Note: Use bupivacaine HCl 0.50% (5mg/ml) injectable solution. ~~Same comment as for lidocaine.~~ **When necessary, bupivacaine may be diluted in 0.9% sodium chloride (isotonic saline solution).**
2025.03.25	Buprenorphine (marmosets) Dose: 0.005 – ~~0.01~~ **0.02** mg/kg Route of administration: IM, SC Frequency: 6-8 hrs (low dose), 8–12 hrs (high dose) Note: Controlled drug.
2025.03.25	Buprenorphine Slow Release (SR) (marmosets) Dose: **0.1-**0.2 mg/kg Route of administration: SC Frequency: 48-72 hrs Note: Buprenorphine SR is a sustained release buprenorphine product that has been developed to provide up to 72 hours of analgesia in NHPs. See administration instructions in section 7.1. Controlled drug.
2025.03.25	**Acetaminophen** (marmosets) **Dose: 6 mg/kg** **Route of administration: PO** **Frequency: 12-24 hrs**
2025.03.25	**8.12. Goodroe, A., Fitz, C., & Bakker, J. (2020). Current Topics in Marmoset Anesthesia and Analgesia. ILAR journal, 61(2-3), 218–229. https://doi.org/10.1093/ilar/ilab001**
2025.05.07	**8.13. Canadian Council on Animal Care. (2025). CCAC guidelines: Scientific procedures (Part B – Analgesia, anesthesia, and surgery).**