DIVISION OF ANIMAL RESOURCES EMORY

The Use of Analgesics in Rodents and Rabbits

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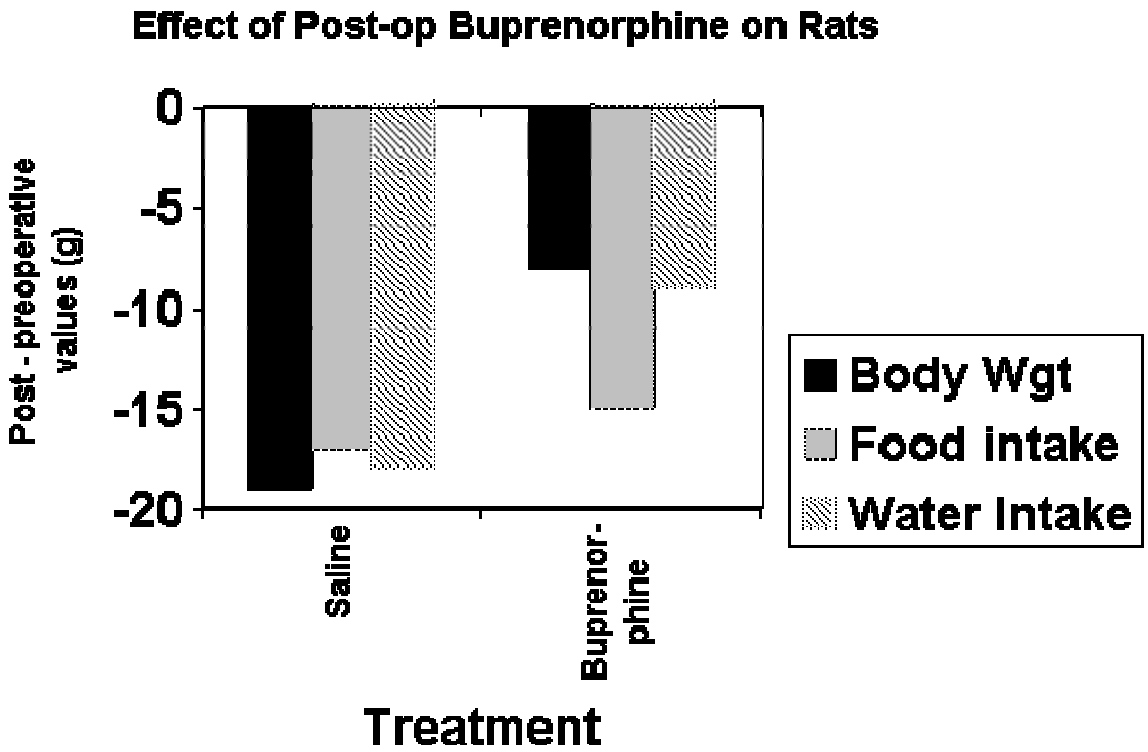
Rationale. Well-established studies have shown repeatedly that effective analgesia enhances locomotion, increases appetite, and reduces the time of postoperative recovery for humans, rodents, rabbits, which are particularly sensitive to pain and inflammation, and other species. The figure below, derived from Liles and Flecknell (1999) illustrates the value of post-operative analgesics in improving recovery of rodents in the first 24 hours following laparotomy. Weight loss and decreases in appetite and water consumption were less in rats given an analgesic agent (buprenorphine) than those given saline. As a general rule, for maximal effectiveness, analgesics should be first administered before the animal is fully recovered from anesthesia and should be continued for the next 48-72 hours. However, as little as a single post-operative dose, in many circumstances, is sufficient to dramatically and positively influence recovery.



Mechanism of Action. Analgesics can act through several mechanisms. Centrally-acting agents, such as morphine, meperidine, codeine, nalbuphine and buprenorphine, interact with the endogenous opioid systems in the CNS. Substances that act locally at the nociceptor, such as local anesthetics, antihistamines, and alpha-2 adrenoreceptor agonists (i.e. xylazine, clonidine, metomidate), block nerve impulses. Nonsteroidal anti-inflammatory drugs (NSAID), such as aspirin, flunixin meglumine and acetaminophen, inhibit the production of the chemical mediators that activate peripheral nociceptors.

Nonsteroidal Anti-Inflammatory Drugs. NSAIDs are sufficiently potent to treat musculoskeletal, incisional, and acute, mild visceral pain. They inhibit the production of metabolic products of arachidonic acid (prostaglandins, prostacyclin) which are potent chemical mediators of inflammation that activate peripheral nociceptors. Because of different sites of action, these agents are synergistic with opioids. However, combinations of NSAIDs should not be used together as they may cause gastritis/gastric ulceration, or renal failure. Platelet inhibition is also a risk especially with agents with cyclooxygenase I activity. Carprofen (Zenecarp) has low cyclooxygenase 1 inhibitory effects and a low potential for renal or gastric toxicity (safer than flunixin). It is very effective when combined with opioids or buprenorphine and has a 24-48 hour duration of efficacy in most species.

Opioids. For the control of acute or chronic visceral pain, opioids are the most powerful and effective analgesics. Bradycardia, respiratory depression, excessive sedation, nausea, ileus and pica may be side effects. Opioid agonist-antagonists, such as buprenorphine, have minimal side effects. Opioids and opioid agonist-antagonists may increase CSF pressure and should be used with caution in craniotomy cases. In addition, the use of most of these agents is strictly controlled by the federal government requiring specialized licensure and the need to record every drop used. The use of traditional, parenterally-administered opioid analgesics such as morphine, meperidine and pentazocine are impractical in rabbits and rodents because of their high metabolic rates which necessitates intensive dosing schedules to maintain therapeutic blood concentrations. Liposome-encapsulated opioid preparations have been reported in rats, along with recipes for generating them, a formulation that may provide analgesia for as long as 7 days with a single injection (Smith et al., 2003). The administration of NSAIDS concomitantly with opioids may allow the effective use of lower doses of opioids with fewer side effects and adequate pain management.

Oral Administration of Analgesic Agents. Voluntary oral consumption of drugs may be impeded by palatability, xenophobia, pain/discomfort, and recovery from anesthesia and generally is ineffective for immediate post-operative use. In addition, consumption of agents may be influenced by diurnal behavioral rhythms (nocturnal consumption is likely to be greater than that during daylight). Oral doses of these agents may be substantially higher than parenteral doses due to first pass effects through the liver (i.e., oral doses of buprenorphine and butorphanol are 10 times that of injected doses). Many orally administered agents are only adequate for controlling low grade pain and some agents, such as acetaminophen, have little oral potency in rodents. An innovative way of providing oral analgesics to rodents is via flavored gelatin. Grape, currant or cherry-

flavored gelatins containing drugs such as ketoprofen (0.4 mg/ml of gelatin) can be administered to rats and mice. Feed 2 ml of gelatin per 200 gram rat once daily. Feeding the gelatin without drugs for a few days conditions the animals to readily accept the drug-impregnated gelatin later. For some drugs, i.e. buprenorphine, the necessary quantity of drug required makes the gelatin unpalatable. In cases where medication is to be delivered in the drinking water, administration for a few days prior to surgery may address the neophobic response. Ultimately, gavage is the only route by which administration of appropriate doses of oral medications can be ensured.

Common Analgesic Doses (in mg/kg) for Rodents and Rabbits

Agent	Guinea Pig	Mouse	Rat	Rabbit
Acetaminophen	----	----	----	1 ml elixir in 100ml drinking water
Aspirin	87 PO BID	100-120 PO BID	100-120 PO BID	100 PO BID
Buprenorphine	0.05 SC q 8-12 hr	0.05-0.1 SC q 8-12 hr	0.01-0.1 SC q 6-12 hr 5-10 PO q 12 hr	0.01-0.05 SC q 8-12 hr
Butorphanol	----	1-5 SC q 4-6 hr	2 SC q 4-6 hr	0.1-0.5 SC q 4-6 hr
Carprofen (Rimadyl)	----	----	5 SC BID	1.5 PO BID
Flunixin meglumine (Banamine)	----	2.5 SC BID	2.5 SC BID	1.1 SC SID-BID
Ibuprofen	----	40/day in drinking water	15/day in drinking water	----
Ketoprofen	----	----	2 PO SID	3 IM BID

Ketorolac	----	5.0-10.0 PO SID	3-5 PO SID-BID 1 IM SID-BID	----
Meloxicam		1 mg/kg SC or PO q 24 hr*	1 mg/kg SC or PO q 24 hr	
Meperidine	10-20 SC q 2-3 hr	10-20 SC q 2-3 hr	5-10 SC q 2-3 hr	5-10 SC q 2-3 hr; 0.2 mg/ml in drinking water
Morphine	2-5 SC q 2-4 hr	2.5 SC q 2-4 hr	2.5 SC q 2-4 hr	2-5 SC q 2-4 hr
Morphine (liposome encapsulated)			2.8 SC once	
Nalbuphine	1-2 q 4-8 hr	4-8 SC q 4-8 hr	1-2 SC q 4-8 hr	1-2 SC q 4-8 hr
Oxymorphone	----	0.1 SC q 4 hr	0.3 SC q 4 hr	----
Oxymorphone (liposome encapsulated)			1.2 SC once	
Pentazocine	----	10 SC q 3-4 hr	10 SC q 4 hr	5-10 SC q 2-4 hr
Xylazine	----	-----	5-12 SC q 2 hr	----

In mice, it is recommended to dilute injectable meloxicam to a concentration of 0.5 mg/ml.

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