Scand. J. Lab. Anim. Sci. No. 1. 2002. Vol. 29

Pain Alleviation in Laboratory Animals
Methods commonly used for perioperative pain-relief

by *Outi Vainio*[1], *Carmela Hellsten*[2], *and Hanna-Marja Voipio*[3]
[1]University of Helsinki, Veterinary Faculty, Department of Clinical Sciences, Hämeentie 57, FIN-00014 University of Helsinki, Finland. [2]Ministry of Agriculture and Forestry, Veterinary and Food Department, P.O.Box 30, FIN-00023 Government, Helsinki, Finland. [3]University of Oulu, Laboratory Animal Centre, P.O.Box 5000, FIN-90014 University of Oulu, Finland .
Correspondence: Outi Vainio, [1]University of Helsinki, Veterinary Faculty, Department of Clinical Sciences, Hämeentie 57, FIN-00014 University of Helsinki, Finland

Pain as a physical and psychological phenomenon

Pain is often defined as an unpleasant sensory or emotional experience associated with actual or potential tissue damage (*IASP, 1979*). It is a subjective experience accompanied by feelings of fear, anxiety, and panic (*Heavner, 1996*). Pain sensation includes the information that a harmful process exists somewhere in the body and an avoidance response should be used to minimize the traumatic effect. Accordingly, the sense of pain is considered essential for the survival of an individual organism. Even though pain has an alarming and protective purpose, intensive or long lasting pain is a strong stressor which may result in individual distress and maladaptive behaviour (*ACVA Position Paper, 1998*).

Tissue damage may have several initiators, such as surgical intervention, traumatic injury, chemical spillage (poisons, toxins), extreme physiological conditions (heat, cold), mechanical pressure or lack of oxygen. A sudden exposure to this kind of initiator may induce acute pain which is short in duration. Acute pain varies in severity from mild to severe and it is usually alleviated by analgesic drugs. The intensity of acute pain following tissue damage is greatest within the first three days (*ACVA Position Paper, 1998*). If pain, for any reason, persists for months or years, it is called chronic or persistent pain. (*ACVA Position Paper, 1998*). Chronic pain is seldom permanently alleviated by analgesics (*Heavner, 1996*).

Pain is divided into somatic (superficial or deep) and visceral pain (*Danneman, 1996*). Somatic superficial pain mainly arises from the skin. It is sharp and well localized. Somatic deep pain has its origin in the muscles, joints, tendons, bones and viscera. It is less sharp and more aching in its nature. Visceral pain differs from somatic pain. It is diffuse and cannot be localized to particular organs or types of injurious stimulation, such as burning.

Pain consists of three components: firstly, transmission of the ascending signal initiated by the tissue injury and, secondly, perception of the signal as an unpleasant experience in the central nervous system. Thirdly, the animal's response to the pain sensation (*Livingstone & Chambers, 2000*). Both the transmission and perception of pain can be modified by drugs.

Local anasthetics nullify the reaction of the pain receptors (unorganized ends of pain neurons) to painful stimulus, or by preventing the signal transmission in the pain neurons. Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) act both peripherally and centrally. Sedatives (tranquilizers) and anasthetics usually have their site of action in the central nervous system by modifying the pain perception to be sensed as less unpleasant. Glucocorticoids and other drugs affecting the various stages of inflammation also have analgesic properties.

Clinical signs of pain

Recognition and quantification of pain in animals remains a difficult task as they cannot verbalize their sensations. The responses of animals to noxious stimuli are determined by evolutionary process. These responses are modulated by individual experience and may be influenced by the surroundings. The assessment of the severity

of pain in animals is based on observation of the behavior of the animals (*Livingstone & Chambers, 2000*).

Pain behaviour has species-specific characteristics but it also varies between individuals within one species. It is important to be accustomed to the normal behaviour of the species in use. In addition, prey animals have adapted the ability to hide signs of pain as a mechanism of survival. The physical appearance of an unprovoked animal reveals a lot to an experienced observer. The technicians who observe the animals on a regular daily basis, are often the persons most familiar with the behavioral variations between the individuals. Thus, their observations should not be neglected when evaluating the welfare or suffering of laboratory animals.

The following indicative behaviors should be observed in animals suspected of suffering from pain: appearance, posture, ambulation, level of activity, unprovoked behaviour, grooming behaviour, appetite, water consumption, defecation, urination, facial expression, reaction to stimulus, and vocalisation. Animals may also express unusual behaviour (teeth grinding in rabbits) or self-mutilation, such as licking, biting or scratching of a painful area.

When pain medication should be used

There is no ultimate evidence that animals sense pain in the same way as humans. However, since the peripheral mechanisms for detection of potentially painful stimuli are similar in animals and man, it is plausible to assume that nervous arousal would be similar (*Hellebrekers, 2000*). Accordingly, procedures that are painful in humans are probably painful in animals even though they seem to recover from certain surgical operations more quickly than humans.

Usually it is easy to assess when animals are suffering from intense or moderate pain as the deviation from normal behaviour is readily observed. However, mild pain may not necessarily change normal behaviour enough that it can be clearly distinguished. A rule of thumb is that analgesics should be given in every case where there is any reason to suspect that an animal is in pain; for example routinely after an operative procedure. Pain should be treated in all animals regardless of the species or body size. Adequate alleviation of pain should result in a return of normal behaviour. Unchanged abnormal behaviour would indicate either an ineffective drug or an initially painless animal. Despite the ethical and practical importance of pain medication, it should be kept in mind that unnecessary analgesics may have harmful effects which outweigh any benefits they confer.

Treatment of chronic pain

Information on chronic pain treatment in animals is limited. Clinical examples of chronic pain include arthritis and chronic lameness (*Brearley & Brearley, 2000*). Also pain induced by a tumor or cancer may be of a chronic nature (*Brearley & Brearley, 2000*). Opioids and NSAIDs have been used in treating animals suffering from chronic pain. In these cases, the drug usually has to be administered for a longer period than recommended in the product information and, therefore, could result in adverse effects (for more details, see Table 1). It is anecdotally known from the experience of the authors that buprenorphine (an agonist-antagonist opioid) has been used to treat pain in laboratory animals over several weeks.

The mode of administration of analgesics requires some thought, especially in the case of a long term dosing schedule. Comparing oral administration to parenteral injections (iv, im, sc, ip), the oral route is usually considered less laborious to the personnel and might be less stressful for the animal itself. The hypodermic needle penetrating the skin and the drug solution stretching the surrounding tissues may induce some pain. Tissue irritating drugs should not be used. In addition, it is known that catching and handling of animals may be more stressful than the injection itself. Based on this information, it is easy to conclude that the oral route of administration is preferred.

A mixture of drugs and water to deliver an analgesic is an option but animals may not consume substances with a strange odor or taste. Drugs can be mixed in food items, such as gelatin. Analgesic-medicated food is also available commercially for certain species. The more severe the pain, the less the animal will consume water and food. Dosing drugs in food is inaccurate

Table 1. Comparison of the clinical efficacy and adverse effects of opioids and NSAIDs in laboratory animals

	OPIOIDS	**NSAIDS**
Mechanism of action.	Distinct receptor [μ- (OP3), δ- (OP1), κ- (OP2)] activation.	Inhibit cyclo-oxygenase isoenzymes (COX-1, COX-2).
Effect on anaesthesia.	Delay recovery.	Do not affect recovery.
Pain intensity used to treat.	Severe pain.	Low or moderate pain.
Effect on heart rate.	May reduce.	No effect.
Effect on blood pressure.	May reduce.	No effect.
Effect on respiratory rate.	All opioids depress respiratory function.*	No effect.
Effect on body temperature.	May potentiate the hypothermic effect of anaesthetics.	Antipyretic effect. No effect on the hypothermic effect of anaesthetics.
Effect on endotoxemia.	No effect.	Alleviate symptoms.
Other effects.	May have euphoric effects.	Anti-inflammatory properties.
Supplemental dosing.	Dose of agonist-antagonists (buprenorphine, butorphanol) should not be repeated.	Dosage can be topped up.
Most severe adverse effects in clinical use.	Respiratory depression, reduced intestinal motility.	Gastrointestinal irritation and bleeding, renal failure.
Special antagonist.	Naloxone.	Not available.
Concomitant use with other analgesics.	Should not be combined with other opioids. Can be combined with NSAIDs.	Should not be combined with other NSAIDs. Can be combined with opioids.
Pre-emptive analgesia.	Effective.	Effective. Many NSAIDs may sensitize kidneys to harmful effects of hypoxia.**
Other remarks.	Drug abuse possible. (Usage legally regulated.)	No social problems.

*Buprenorphine has the least depressive effect on respiration.

**Carprofen is presently consided as a safe NSAID for pre-emptive use.

especially in group-housed animals. Some drugs may not be stable in water or exposure in light. To ensure accurate dosing it might be preferrable to inject the drug. Alternatively, if the treatment schedule continues for weeks, the most painful period could be covered by injections and, when the animals recover (as they do postoperatively), therapy could be continued orally.

Humane endpoints

Experiments supposed to induce pain and distress to animals should include a previously determined severity limit scoring system. When the criteria for one or more limit points are fullfilled, the animal should be euthanized regardless of the phase of study. These severity limits or humane endpoints are the utmost limit of pain, distress, suffering or any other harm that one animal may be permitted

to experience. A detailed description of the humane endpoints has been presented by Jones *et al.* (*1998*). In many species the correlation between the loss of body weight (in comparison with control animals) can be used as an example of a humane endpoint. Loss of body weight up to 10 % is of mild severity; 10 – 25 % weight loss is moderate and more than 25 % weight loss is considered substantial. Accordingly, an animal which has lost more the 25 % of the body weight should be euthanized (*Jones et al., 1998*). When using body weight as a sign of wellbeing, the kind of procedure performed must be taken into consideration, and also if the animals are growing. A certain percentage of body weight reduction is more severe in a growing animal. In addition to weight loss, other criteria may sometimes be used to determine humane end points; e.g. in neoplasia studies, tumor size. Thus the intramural animal care and use program of the National Institutes of Health in the United States of America states that a mean tumor diameter should not exceed 20 mm in an adult mouse, or 40 mm in an adult rat. However, it should be noted that using these criteria may not always give a true indication of painfulness as a smaller tumor may still press against a neuron or other sensitive organ and, therefore, be more painful than a large lump in the skin or other loose tissue.

Pain in anaesthetized animals

It is of great importance to note that an anaesthetized animal is able to sense pain even though it does not show it by any movements or vocalization. Increased heart rate, blood pressure and respiratory frequency in an anaesthetized animal may indicate that it is experiencing pain. In such cases, the anasthetic regimen should be immediately checked, the anasthetic level deepened if not contraindicated, or additional analgesic drugs administered.

Pain in young animals

Newborn animals, like human babies, react to painful stimuli by vocalization and often by violent movements, increased heart rate and increased blood pressure. These reactions are interpreted as signs of a pain sensation (*Owens & Todt. 1984*). Accordingly, adequate pain treatment should be available also to them. In human infants, opioids, such as fentanyl, have been successfully used for pain alleviation.

Most dose recommendations of analgesic drugs are intended for adult animals. Therefore, it may be difficult to find accurate dose recommendations for very young animals. The doses needed may be either lower or higher than those for adults.

There is no confident information whether foetuses sense noxious stimuli. To avoid any painful interventions, it is proposed that operations on foetuses should be avoided during the last trimester of pregnancy in cases when no analgesics or anasthetics are used.

Pain in genetically modified animals

The number of genetically manipulated animals has increased enormously during the last years. Most of the genetic recombinations are harmless to the animals. However, it must be admitted that our knowledge of the effect of the genetic manipulations on the wellbeing of the animals is incomplete. In accordance with the present EU legislation, it could be concluded that gene modifications that induce suffering to the animal are not acceptable without a special medical reason. It is beyond the professional experience of the authors to characterise when genetically manipulated animals might be suffering from pain.

Pharmacological control of perioperative pain

In recent years, it has been observed that changes in the central processing of the ascending pain signals is suppressed to a greater extent when the analgesic is administered prior to the induction of the pain-inducing stimulus; a phenomenon termed pre-emptive analgesia (*Dobromylskyj et al., 2000*). Animals treated with analgesics before any incision or painful injection, experience less pain postoperatively and require less post-operative analgesics. If pre-emptive medication, for whatever reason, cannot be utilized, analgesic medication should be given at the end of the operation and definitely before the return of consciousness.

Pain transmission involves a multiplicity of pathways and central processing. Therefore, it is not surprising that good clinical effect is obtained with a multi-modal pain therapy, which means that

two drugs with different mechanisms of action are concomitantly used (*Dobromylskyj et al., 2000*). In these combinations, the most common drugs of choice are opioids and NSAIDs. A comparison of the pharmacological characteristics of both drug groups is presented in Table 1.

Opioids

Opioids, with morphine being the reference substance, are a group of natural alkaloids and synthetic drugs which are considered as the most powerful analgesics available. Opioids have relatively short half-lives and usually require supplemental dosing (*Heavner, 1996*). The analgesic effect of opioids is mainly mediated via μ-receptors but the δ- and κ-receptors are also involved (*Short & Otto, 1996*). One of the most severe side effects of opioids is respiratory depression even though its significance may have been overestimated in animals when compared to humans. Opioids potentiate the effect of the anaesthetic drugs. In anaesthetized animals, this is seen as a prolonged recovery time.

Pharmacologically, based on receptor activity, opioids are classified as agonists (morphine, pethidine, fentanyl, codeine, methadone, sufentanil, alfentanil, oxymorphone), agonist-antagonists (buprenorphine, butorphanol, pentazocine, nalbuphine, nalorphine) or pure antagonists (naloxone, naltrexone). The opioids used as analgesics are either agonists or agonist-antagonists (*Short & Otto, 1996*). It is necessary to note that agonist-antagonists, such as buprenorphine, cannot be titrated up to effect. From clinical experience, we know that repeated administrations of small buprenorphine doses may in certain situations behave as an antagonist, resulting in the abolishment of any remaining analgesia or even causing hyperalgesia. Thus, if buprenorphine is used, the confirmed dose recommendation should be strictly followed. Dose recommendations are given in Table 2.

If opioids are used as a part of balanced anesthesia, the recovery of the animals may be hastened by using opioid antagonists (naloxone). Sometimes there may be a need to alleviate the adverse effects (e.g. respiratory depression) induced by opioids. If naloxone is used to antagonise the drug effect, it will also reverse the analgesic effect of the drug and the animals will wake up to sense intensive pain if painful procedures have been performed. In such cases, analgesics with other mechanism of action (such as NSAIDs) should be used.

NSAIDs

NSAIDs inhibit the isoenzymes of cyclo-oxygenase (COX-1 and COX-2), thus preventing the metabolism of arachidonic acid which leads to the formation of prostaglandins, prostacyclin, thromboxane, and leucotrienes. Prostaglandins (PGE_2 and PGI_2) are particularly involved in the enhancement of painful stimuli by sensitizing the pain receptors to the action of the mediators of inflammation, such as bradykinin and histamine (*Nolan, 2000*). Accordingly, the cyclo-oxygenase inhibitors alleviate the symptoms of both inflammation and pain. NSAIDs do not potentiate the effects of the anasthetics and, therefore, they do not prolong the recovery time. For dose recommendations, see Table 3.

NSAIDs have a ceiling effect: an increase in the dose potentiates the analgesic efficacy to a certain level. A still higher dose enhances the risk for adverse reactions without providing any analgesic benefit. Concomitant use of two or more NSAIDs does not potentiate clinical efficacy but increases the number of side effects. In all species, dose recommendations should be strictly followed.

Local anaesthetics

Local anaesthetics, such as lidocaine, bupivacaine, mepivacaine, and ropivacaine, are effective substances for perioperative pain management (*Nolan, 2000*). They can be used pre-emptively before the onset of tissue damage or intraoperatively to provide a better analgesia in anaesthetised animals. Local anaesthetics have also been employed to control postoperative pain.

Local anaesthetics can be administered topically around an exposed nerve or introduced around the surgical site. They also can be infiltrated along a line to block nerves supplying the region to be operated. Intravenous regional anaesthesia is created when the analgesic drug is administered into a distal vein where the venous circulation is limited with a proximal tourniquet. While this is a common method of regional anaesthesia in

Table 2. Opioids used to alleviate pain in the most common laboratory animals. Respiratory depression is considered as the most serious side effect. Opioids may also reduce heart rate and blood pressure. They potentiate the effect of the anaesthetic drugs. In anaesthetized animals, there is seen as a delayed recovery.

Drug	**Species**	**Dose (mg/kg)**	**Route**	**Frequency**	*Reference*
Buprenorphine	Rat	0.01-0.1	SC	8-12 h	Liles & Flecknell 1993 Liles & Flecknell 1994 Flecknell 1996 Abbott & Bonder 1997 Hayes & Flecknell 1999
		0.01-0.05	IV	8-12 h	Flecknell 1996
		0.1-0.3	PO	8-12 h	Flecknell 1996 Flecknell et al. 1999a
	Mouse	0.05-0.1	SC	12 h	Flecknell 1996
	Rabbit	0.01-0.05	SC, IM	8-12 h	Jenkins 1987 Flecknell 1996
		0.01-0.05	IV	6-12 h	Flecknell & Liles 1990 Flecknell 1996
	Guinea pig	0.05	SC	8-12 h	Jenkins 1987 Flecknell 1996
	Pig	0.005-0.01	IM	12 h	Jenkins 1987 Sager 1993
		0.1	IM	12 h	Randolph 1994
		0.005-0.02	IM, IV	6-12 h	Flecknell 1996
	Dog	0.005-0.02	SC, IM, IV	4-12 h	Jenkins 1987 Bednarski 1989 Sager 1993 Brock 1995 Flecknell 1996 Hansen 1997 Hellyer & Gaynor 1998 Carroll 1999
	Cat	0.005-0.02	SC, IM, IV	4-12 h	Jenkins 1987 Bednarski 1989 Sager 1993 Brock 1995 Flecknell 1996 Haas & Svendsen 1997 Hansen 1997 Hellyer & Gaynor 1998 Carroll 1999

Butorphanol	Rat	0.05-2.0	SC	4 h	Jenkins 1987 McKellar 1989 Flecknell 1996
	Mouse	0.05-5.0	SC	4 h	Jenkins 1987 Flecknell 1996
	Rabbit	0.1-0.5	IV	1.5-5	Flecknell & Liles 1990 Flecknell 1996
	Dog	0.2-0.5	SC, IM, IV	1-4 h	Jenkins 1987 Bednarski 1989 Sager 1993 Brock 1995 Flecknell 1996 Hansen 1997 Pollet et al. 1998 Sawyer 1998 Carroll 1999
		0.2-0.5	IV	0.25-1 h	Hellyer & Gaynor 1998
	Cat	0.1-0.4	SC, IM, IV	2-6 h	Jenkins 1987 Sager 1993 Brock 1995 Flecknell 1996 Hansen 1997 Pollet et al. 1998 Carroll 1999
		0.1-0.2	IV	0.25-1 h	Hellyer & Gaynor 1998
		0.5-4.0	PO	6-8 h	Hansen 1997 Carroll et al. 1998
Codeine	Rat	25-60	SC	4 h	Jenkins 1987 McKellar 1989
	Mouse	10-20	SC		Jenkins 1987 McKellar 1989
		60-90	PO		Jenkins 1987
	Rabbit	10	IV, PO		Benson et al. 1990 Borchard et al. 1990
	Guinea pig	25	SC		McKellar 1989
Methadone	Rabbit	1.0	IV		Piercey & Schroeder 1980
	Guinea pig	3.0-6.0	SC		Jenkins 1987
	Dog	0.1-1.0	SC, IM	2-6 h	Wright et al. 1985 Hellebrekers 1990

					Haas & Svendsen 1997
	Cat	0.05-0.2	SC, IM	2-6 h	Hellebrekers 1990 Haas & Svendsen 1997
		0.1	IV		Haas & Svendsen 1997
Morphine	Rat	2.5	SC	2-4 h	Flecknell 1996
		10.0	SC	2-4 h	Jenkins 1987 McKellar 1989 Wixson & Smiler 1997
	Mouse	2.5	SC	2-4 h	Flecknell 1996
		10.0	SC	2-4 h	Jenkins 1987 McKellar 1989
	Rabbit	2.0-10.0	SC, IM	2-4 h	Jenkins 1987 McKellar 1989 Benson et al. 1990 Borchard et al. 1990 Wixson 1994 Flecknell 1996
	Guinea pig	10.0	SC, IM	2-4 h	Jenkins 1987 McKellar 1989
		2.0-5.0	SC, IM	4 h	Flecknell 1996
	Pig	0.2-1.0	IM	3-4 h (maximum dose 20 h)	Jenkins 1987 Sager 1993 Flecknell 1996
	Dog	0.1-2.0	SC, IM	2-6 h	Bednarski 1989 Brock 1995 Haas & Svendsen 1997 Hellyer & Gaynor 1998 Sawyer 1998
		0.5-5.0	SC, IM	4-6 h	Jenkins 1987 Flecknell 1996
		0.1-1.0	IV	1-4 h	Haas & Svendsen 1997 Hellyer & Gaynor 1998
		1.0-5.0	PO	4-6 h	Hansen 1997
	Cat	0.1-0.5	SC, IM	2-6 h	Jenkins 1987 Brock 1995 Flecknell 1996 Hansen 1997 Hellyer & Gaynor 1998 Sawyer 1998

		0.05-0.4	IV	1-4 h	Hansen 1997 Hellyer & Gaynor 1998
Nalbuphine	Rat	1.0-2.0	IM	3 h	Flecknell 1996
	Mouse	4.0-8.0	IM		Flecknell 1996
	Rabbit	1.0-4.0	IV	4-6 h	Flecknell & Liles 1990 Flecknell 1996
	Guinea pig	1.0-2.0	IM, IV, IP		Flecknell 1996
	Dog	0.5-2.0	SC, IM, IV	3-4 h	Jenkins 1987 Bednarski 1989 Flecknell 1996 Hansen 1997
	Cat	1.5-3.0	IV	3 h	Flecknell 1996
Oxymorphone	Rat	0.2-0.3	SC	4 h	Wixson & Smiler 1997
	Rabbit	0.2	IM		Wixson 1994
	Dog	0.02-0.2	SC, IM, IV	2-6 h	Wright et al. 1985 Bednarski 1989 Brock 1995 Flecknell 1996 Hansen 1997 Hellyer & Gaynor 1998 Sawyer 1998 Carroll 1999
	Cat	0.02-0.2	SC, IM, IV	2-6 h	Bednarski 1989 Brock 1995 Flecknell 1996 Hansen 1997 Hellyer & Gaynor 1998 Carroll 1999
Pentazocine	Rat	10	SC	3-4 h	Jenkins 1987 McKellar 1989 Flecknell 1996
	Mouse	10	SC	3-4 h	Jenkins 1987 McKellar 1989 Flecknell 1996
	Rabbit	5-20 5	SC, IM IV	4 h 2-4 h	Jenkins 1987 McKellar 1989 Flecknell 1996 Flecknell et al. 1989 Flecknell & Liles 1990

					Flecknell 1996
	Pig	2.0	IM, IV	4 h	Jenkins 1987 Sager 1993 Flecknell 1996
	Dog	1.0-3.0	SC, IM, IV	4-6 h	Jenkins 1987 Johnson 1991 Sager 1993 Flecknell 1996 Hansen 1997 Sawyer 1998
		1.0-4.0	IM, IV	0.5-1 h	Bednarski 1989
		2.0-15.0	PO	4-8 h	Jenkins 1987 Sager 1993 Hansen 1997
	Cat	1.0-4.0	SC, IM, IV	4 h	Jenkins 1987 Johnson 1991 Sager 1993
		1.0-4.0	IM, IV	0.5-1 h	Bednarski 1989
Pethidine	Rat	10-20	SC, IM	2-3 h	Jenkins 1987 McKellar 1989 Flecknell 1996
	Mouse	10-20	SC, IM	2-3 h	Jenkins 1987 McKellar 1989 Flecknell 1996
	Rabbit	10-20	SC, IM	2-3 h	Jenkins 1987 McKellar 1989 Flecknell 1996
	Guinea pig	10-20	SC, IM	2-3 h	Jenkins 1987 McKellar 1989 Flecknell 1996
	Pig	2.0	IM, IV	2-4 h	Jenkins 1987 Sager 1993 Flecknell 1996
	Dog	2.0-10.0	SC, IM	2-3 h	Jenkins 1987 Flecknell 1996
		1.0-6.0	IM	0.5-1 h	Bednarski 1989 Brock 1995 Haas & Svendsen 1997
	Cat	2.0-10.0	SC, IM	2-3 h	Jenkins 1987 Flecknell 1996

		1.0-3.0	IM	6-8 h	Haas & Svendsen 1997
		1.0-6.0	IM	0.5-1 h	Bednarski 1989 Brock 1995

Table 3. Nonsteroidal anti-inflammatory drugs used in the most common laboratory animals. Gastrointestinal ulceration and anaesthesia related acute renal failure are the most common side effects. NSAIDs have only minor effect on the cardiovascular system and they do not delay recovery from anaesthesia.

Drug	**Species**	**Dose (mg/kg)**	**Route**	**Frequency**	*Reference*
Acetaminophen (paracetamol) Note – this drug does not have any significant anti-inflammatory effects.	Rat	200 200	PO IP	4 h	Jenkins 1987 McKellar 1989 Liles & Flecknell 1992 Flecknell 1996 Cooper et al. 1997
	Mouse	200-300 300	PO IP	4 h	McKellar 1989 Liles & Flecknell 1992 Flecknell 1996 Jenkins 1987
	Rabbit	200-500	PO	6 h	Patil 1997
	Dog	10-15	PO	6-12	Nap 1993 Sager 1993 Flecknell 1996 Hansen 1997
Aspirin (acetylsalicylic acid)	Rat	100 80	PO IP	4 h	Jenkins 1987 McKellar 1989 Liles & Flecknell 1992 Flecknell 1996 Sahni & Srivastava 1992
	Mouse	120	PO	4 h	Jenkins 1987 McKellar 1989 Liles & Flecknell 1992 Flecknell 1996
	Rabbit	100	PO		Koch & Dwyer 1988 Flecknell 1996
	Guinea pig	87	PO		Albengres et al. 1988 Flecknell 1996
	Pig	10	PO	4 h	Jenkins 1987

					Sager 1993 Randolph 1994
	Dog	10-25	PO	8-12 h	Jenkins 1987 Bednarski 1989 Hellebrekers 1990 Nap 1993 Sager 1993 Flecknell 1996 Haas & Svendsen 1997 Hansen 1997
	Cat	10 10-25	PO PO	48 h 48 h	Jenkins 1987 Bednarski 1989 Nap 1993 Sager 1993 Haas & Svendsen 1997 Flecknell 1996 Hansen 1997
Carprofen	Rat	5.0	SC, PO	24 h	Liles & Flecknell 1994 Flecknell 1996 Flecknell et al. 1999b Dobromylskyj et al. 2000
	Mouse	5.0	SC, PO	24 h	Dobromylskyj et al. 2000
	Rabbit	2.0-4.0 1.5	SC, PO PO	12-24 h 12 h	Ramer et al. 1999 Flecknell 1996
	Pig	2.0-4.0	SC, IV	24 h	Flecknell 1996
	Dog	4.0 4.0 1.0-2.0	SC, IV SC, IM, IV, PO PO	24 h initial dose, then 2.2 q 12 h 12 h (max 7 days)	Flecknell 1996 Mathews 1996 Flecknell 1996 Hansen 1997

					Hellyer & Gaynor 1998
	Cat	4.0 4.0	SC, IM, IV, PO SC	initial dose, then 2.2 q 12 h	Mathews 1996 Lascelles et al. 1995 Flecknell 1996 Balmer et al. 1998
Diclofenac	Rat	10	PO		Flecknell 1996
	Mouse	8-14	PO		Walter et al. 1989 Flecknell 1996
	Guinea pig	2.1	PO		Albengres et al. 1988 Flecknell 1996
Flufenamic acid	Rat	5.0	PO		Liles & Flecknell 1992
	Guinea pig	30	PO		Wilhelmi 1974
Flunixin	Rat	2.5 1.1	SC, IM IM		Liles & Flecknell 1992 Flecknell 1996 McKellar 1989
	Mouse	2.5	SC, IM		Liles & Flecknell 1992 Flecknell 1996
	Rabbit	1.1	SC, IM		McKellar 1989 More et al. 1989 Flecknell 1996
	Pig	1.0-2.0	SC, IV	24 h	Flecknell 1996
	Dog	0.5-1.0 0.5-1.0	SC, IM, IV PO	24 h (max 3 days) 24 h (max 3 days)	Bednarski 1989 Sackmann 1991 Nap 1993 Mathews 1996 Haas & Svendsen 1997 Hansen 1997 Sager 1993

					Flecknell 1996 Haas & Svendsen 1997
	Cat	0.25-1.0 0.5-1.0	SC IM, IV	12-24 h (max 5 days) 24 h (max 3 days)	Flecknell 1996 Nap 1993
Ibuprofen	Rat	10-30	PO		Jenkins 1987 Liles & Flecknell 1992 Flecknell 1996
	Mouse	7.5 30.0 7.0	PO PO IP		Jenkins 1987 Walter et al. 1989 Liles & Flecknell 1992 Flecknell 1996 Walter et al. 1989
	Rabbit	10	IV		Cominelli et al. 1990 Flecknell 1996
	Guinea pig	10	IM		Flecknell 1996
Indomethacin	Rat	2.0	PO		Liles & Flecknell 1992 Flecknell 1996
	Mouse	1.0-1.5	PO		Walter et al. 1989 Liles & Flecknell 1992 Flecknell 1996
	Rabbit	12.5	PO		Keller et al. 1990 Flecknell 1996
	Guinea pig	2.5 8.0-9.0	PO PO		Wilhelmi 1974 Albengres et al. 1988 Flecknell 1996

Ketoprofen	Rat	5.0	SC		Flecknell et al. 1999b
	Mouse	2.0	PO		Walter et al. 1989
	Rabbit	1.0-3.0	IM		Perrin et al. 1990 Flecknell 1996
	Dog	1.0-2.0 1.0	SC, IM, IV PO	24 h (max 5 days) 24 h (max 5 days)	Flecknell 1996 Haas & Svendsen 1997 Hansen 1997 Hellyer & Gaynor 1998 Flecknell 1996 Mathews 1996 Haas & Svendsen 1997 Hansen 1997 Hellyer & Gaynor 1998
	Cat	1.0-2.0 1.0	SC, IM, IV PO	24 h (max 5 days) 24 h (max 5 days)	Flecknell 1996 Haas & Svendsen 1997 Hansen 1997 Hellyer & Gaynor 1998 Flecknell 1996 Mathews 1996 Haas & Svendsen 1997 Hansen 1997 Hellyer & Gaynor 1998
Ketorolac	Mouse	0.7	PO		Walter et al. 1989
	Dog	0.3-0.5	IM, IV	8-12 h (max 2 doses)	Mathews 1996 Hansen 1997
	Cat	0.25	IM	8-12 h (max 2 doses)	Mathews 1996 Hansen 1997
Naproxen	Mouse	57	PO		Walter et al. 1989

	Guinea pig	15	PO		Albengres et al. 1988
	Dog	5.0	PO	initial dose, then 1.0-2.0 q 24-48 h	Jenkins 1987 Sager 1993 Hansen 1997
		3.0	PO	24 h	Sackmann 1991
Phenylbutazone	Rat	20	PO		Liles & Flecknell 1992
	Mouse	30	PO		Liles & Flecknell 1992
	Rabbit	15	PO		Benson et al. 1990
		100	IV		Borchard et al. 1990
	Guinea pig	40	PO		Wilhelmi 1974
	Pig	2.0-5.0	IV		Randolph 1994
		10	PO	12 h	Sager 1993
	Dog	15-20	IV	8 h	Johnson 1991 Sager 1993
		10-25	PO	8-12 h	Johnson 1991 Sackmann 1991 Nap 1993 Sager 1993 Haas & Svendsen 1997 Hansen 1997
		20	PO	24 h	Bednarski 1989 Hellebrekers 1990
	Cat	4.0-5.0	PO	24-36 h	Sackmann 1991
		10.0-14.0	PO	12 h	Aron 1987 Sager 1993
Piroxicam	Rat	3.0	PO		Liles & Flecknell 1992 Flecknell 1996

	Mouse	3.0	PO		Walter et al. 1989 Liles & Flecknell 1992 Flecknell 1996
	Rabbit	0.2	PO	8 h	More et al. 1989
	Guinea pig	6.0	PO		Albengres et al. 1988 Flecknell 1996
	Dog	0.2-0.4 0.3	IM, PO PO	24 h 48 h	Sager 1993 Flecknell 1996 Mathews 1996 Hansen 1997
Tenoxicam	Rat	10.0	PO		Liles & Flecknell 1992
	Guinea pig	7.2	PO		Albengres et al. 1988

humans, it is uncommon and impractical in most laboratory animal species. Specific nerve blocks abolish nociception from tissues which are nervated by this nerve. Local anaesthetics are also effective when administered epidurally, spinally or into a cavity (*Dobromylskyj et al., 2000*). The clinical techniques for the application of local anaesthetics is beyond the scope of this text.

Postoperative painfulness of various surgical interventions

Animals recover more quickly from painful more quickly when treated with adequate analgesics, such as opioids. Operations on the head (eyes, teeth, ears) and on the anal/rectal area are ranked to be quite painful and, accordingly, proper postoperative analgesia has to be used (opioids or NSAIDs). Different parts of a certain organ can vary in their sensitivities: the cervical vertebrae are considered more sensitive to injury than the distal vertebrae. Orthopedic surgery induces moderate surgical interventions when they are given pre-emptive analgesics and receive adequate postoperative pain alleviation (*Dobromylskyj et al., 2000*). Even though definite ranking lists of the pain potential of various surgical interventions cannot be presented, the Laboratory Animal Science Association has scored scientific procedures on the basis of their severity. This scoring system was published by Wallace *et al.* (*1990*); some interpretations are presented.

Thoracotomy is considered an extremely painful operation in humans but animals seem to recover pain with the exception of hip joint and shoulder joint operations which are considered to be more painful than the others. NSAIDs are usually administered after orthopedic surgery as much to alleviate pain as to prevent inflammation. Limb amputations are always very painful and opioids might be the drug of choice. There is no information on whether animals suffer from post operative phantom pain.

Entitlement of pain medication

There are limits (humane end points) where it is ethically more acceptable to euthanize suffering animals than keep them alive in pain. It is impossible to imagine any medical reasons which would lead us to intentionally keep animals in pain for a shorter or a longer period even when medication is used to alleviate their distress. It is essential to point out that an ethical judgement must precede any with-holding of postoperative or other analgesics. Finally, it is extremely unlikely that any 'results' originating from suffering animals would be scientifically valid.

Acknowledgement

This paper was supported by a grant from by the Scandinavian Society for Laboratory Animal Science.

References

Abbott FV & M Bonder: Options for management of acute pain in the rat. Veterinary Record 1997, *149*, 553-557.

ACVA Position Paper: American college of veterinary anesthesiologists' position paper on the treatment of pain in animals. JAVMA 213, 628-630, 1998.

Albengres E, JL Pinquier, P Riant, F Bree, S Urien, J Barre & JP Tillement: Pharmacological criteria for risk benefit evaluation of NSAIDs. Suppl to Scand J Rheumatology 1988, *73*, 3-5.

Aron DN: Pain. In: Small animal medical diagnosis, 411-424. Lorenz MD & Cornelius LM (eds). Philadelphia etc. JB Lippincott Company 1987, pp 441-424.

Balmer TV, D Irvine, RS Jones, J RobertsJ, L Slingsby, PM Taylors, AE Waterman & C Waters: Comparison of carprofen and pethidine as postoperative analgesics in the cat. J. Small Anim. Pract. 1998, *39*, 158-164.

Benson GJ, JC Thurmon & LE Davis: Laboratory animal analgesia. In: The experimental animal in biomedical research, Vol. 1., Rollin BE and Kesel ML (eds). Boca Raton, Florida, CRC Press, 1990.

Bednarski RM: Anesthesia and pain control. Veterinary Clinics of North America: J. Small Anim. Pract. 1989, *19*, 1223-1238.

Borchard RE, CD Barnes & LG Eltherington: In: Drug dosage in laboratory animals: A handbook, Borchard RE, CD Barnes and Eltherington LG (eds), 3rd ed. Telford, Caldwell, New Jersey, 1990.

Brearley JC & MJ Brearley: Chronic pain in animals. In: Pain management in animals, Flecknell PA and Waterman-Pearsons A (eds), WB Saunders, 2000, 147-160.

Brock N: Treating moderate and severe pain in small animals. Can. Vet. J. 1995, *36*, 658-660.

Carroll GL: Analgesics and pain. Veterinary clinics of North America: J. Small Anim. Pract. 1999, *29*, 701-717.

Carroll GL, LB Howe, MR Slater, L Haughn, EA Martinez, SM Hartsfield & NS Matthews: Evaluation of analgesia provided by postoperative administration of butorphanol to cats undergoing onychectomy. J. Am. Ass. Vet. Med. 1998, *213*, 246-250.

Cominelli F, CC Nast, R Llerena, CA Dinarello & RD Zipser: Interleukin I suppresses inflammation in rabbit colitis mediation by endogenous prostaglandins. J. Clin. Investig. 1990, *85*, 582-586.

Cooper DM, D DeLong & CS Gillett: Analgesic efficacy of acetaminophen and buprenorphine administered in the drinking water of rats. Contemporary Topics in Lab. Anim. Science. 1997, *36*, 58-62.

Danneman JP: Monitoring of analgesia. In: Anesthesia and analgesia in laboratory animals, Kohn DF, SK Wixson, WJ White & GJ Benson (eds), Academic Press, New York, 1996, 83-103.

Dobromylskyj P, PA Flecknell, BD Lascelles, PJ Pascoe, P Taylor & A Waterman-Pearsons: Management of postoperative and other acute pain. In: Pain management in animals, Flecknell PA and Waterman-Pearsons A (eds), WB Saunders, 2000, 81-145.

Flecknell PA: Post-operative care. In: Laboratory animal anaesthesia, ed. 2, 127-157. London, Academic Press, 1996, pp127-157.

Flecknell PA & JH Liles: Assessment of the analgesic action of opioid agonist-antagonists in the rabbit. J Ass. Vet. Anaesth. of Great Britain and Ireland 1990, *17*, 24-29.

Flecknell PA, JH Liles & R Wotton: Reversal of

fentanyl/fluanison neoroleptanalgesia in the rabbit using mixed agonist/antagonist opioids. Lab. Anim. 1989, *23*, 147-155.

Flecknell PA, JV Roughan & R Stewart: Use of oral buprenorphine ('buprenorphine jello') for postoperative analgesia in rats - a clinical trial. Lab. Anim. 1999a, *33*, 169-174.

Flecknell PA, HE Orr, JV Roughan & R Stewart: Comparison of the effects of oral or subcutaneous carprofen or ketoprofen in rats undergoing laparotomy. Vet. Rec. 1999b, *144*, 65-67.

Haas T & O Svendsen: Akut smertebehandling hos hunde og katte. Dansk Veterinaertidsskrift. 1997, *80*, 715-717.

Hansen B: Appendix: Drug dosage recommendations. Seminars in Veterinary Medicine and Surgery (Small Animal) 1997, *12*, 139-142.

Hayes JH & PA Flecknell: A comparison of pre- and post-surgical administration of bupivacaine or buprenorphine following laparotomy in the rat. Lab. Anim. 1999, *33*, 16-23.

Heavner JE: Perioperative pain and distress. In: Lumb & Jones' Veterinary Anesthesia, Thurmon JC, Tranquilli WJ and Benson GJ (eds), 3rd ed., Williams & Wilkins, Baltimore, 1996, 40-60.

Hellebrekers LJ: Post-operative pain relief in companion animals. Tijdschrift voor Diergeneeskunde 1990, *115*, 81S-82S.

Hellebrekers LJ: Pain in animals. In: Animal Pain, Hellebrekers LJ (ed.), Van der Weers, Utrecht, The Netherlands, 2000, 11-16.

Hellyer PW & JS Gaynor: Acute postsurgical pain in dogs and cats. Compendium on Continuing Education for the Practicing Veterinarian. 1998, *20*, 140-153.

IASP Subcommittee on taxonomy. Pain terms: a list of definitions and notes on usage. Pain 1979, *6*, 249.

Jenkins WL: Pharmacological aspects of analgesic drugs in animals: an overview. J. Am. Vet. Med. Ass. 1987, *191*, 1231-1240.

Johnson JM: The veterinarian's responsibility: Assessing and managing acute pain in dogs and cats. Part 2. Compendium on Continuing Education for the Practicing Veterinarian. 1991, *13*, 911-916, 921.

Jones HRP, J Oates & BA Trussell: An applied approach to the assessment of severity. In the Proceedings of the international conference, 22-25 November, Zeist, the Netherlands, 1998, 40-47.

Keller J, P Kjaersgaard-Andersen, I Bayer-Kriestensen & F Melsen: Indomethacin and bone trauma. Effects on remodeling a rabbit bone. Acta Ortopaed. Scand. 1990, 61, 66-69.

Koch KL & A Dwyer: Effects of acetylsalicylic acid on electromechanical activity of in vivo rabbit ileum. Digestive Disease Sciences 1988, *33*, 962-968.

Lascelles BDX, AE Waterman, S Mirchandani & P Cripps: Post-operative carprofen in cats: A dose titration study of the analgesic efficacy of carprofen versus pethidine. J. Vet. Anaesth. 1995, *22*, 32-33.

Liles JH & PA Flecknell: The use of non-steroidal anti-inflammatory drugs for the relief of pain in laboratory rodents and rabbits. Lab. Anim. 1992, *26*, 241-255.

Liles JH & PA Flecknell: The effects of surgical stimulus on the rat and the influence of analgesic treatment. Br. Vet. J. 1993, *149*, 515-525.

Liles JH & PA Flecknell: A comparison of the effects of buprenorphine, carprofen and flunixin following laparotomy in rats. J. Vet. Pharmacol. Therap. 1994, *17*, 284-290.

Livingstone A & P Chambers: The physiology of pain. In: Pain management in animals. Eds PA Flecknell and A Waterman-Pearsons. WB Saunders 2000, 9-19.

Mathews KA: Nonsteroidal antiinflammatory analgesics to manage acute pain in dogs and cats. Compendium on Continuing Education for the Practicing Veterinarian 1996, *18*, 1117-1123.

McKellar QA: Drug dosages for small mammals. In Practice. 1989, *11*, 57-61.

More RC, MH Kody, JM Kabo, FJ Dorey & RA Meals: The effects of two non-steroidal antiinflammatory drugs on limb swelling, joint stiffness, and bone torsional strength following fracture in a rabbit model. Clin. Orthop. 1989, *247*, 306-312.

Nap RC: Non-steroidal anti-inflammatory drugs

(NSAIDs) in companion animal medicine. Tijdschrift voor Diergeneeskunde 1993, *118* Suppl 1, 6S-8S.

Nolan A: Pharmacology of analgesic drugs. In: Pain management in animals, Flecknell PA and Waterman-Pearsons A (eds), WB Saunders, 2000, 21-52.

Owens ME & EH Todt: Pain in infancy: neonatal reaction to a heel lance. Pain 1984, *1*, 77-86.

Patil VU, C Fairbrother & BM Dunham: Endotracheal intubation in the rabbit: A quick, reliable method. Lab. Animal. 1997, *26*, 28-29.

Piercey MF & LA Schroeder: A quantitative analgesic assay in the rabbit based on the response to tooth pulp stimulation. Arch. Internat. Pharmacodyn. 1980, *248*, 294-304.

Perrin A, G Milano, A Thyss, P Cambon, & M Schneider: Biochemical and pharmacological consequences of the interaction between methotrexate and ketoprofen in the rabbit. Br. J. Cancer 1990, *62*, 736-741.

Pollet R, R Claxton & M Raffe: Using butorphanol tartrate to manage pain in cats. Vet. Med. 1998, *93*, 146-155.

Ramer JC, J Paul-Murphy & KG Benson: Evaluating and stabilizing critically ill rabbits - part II. Compendium on Continuing Education for the Practicing Veterinarian 1999, *21*, 116-125.

Randolph MM: Post-operative care and analgesia of farm animals used in biomedical research. Animal Welfare Information Center Newsletter 1994, *5*, 11-13.

Sackman JE: Pain. Part 2. Control of pain in animals. Compendium on Continuing Education for the Practicing Veterinarian 1991, *13*, 181-187, 190-193.

Sager M: Schmertzprophylaxe und Schmerztherapie bei kleinen und grossen Haustieren. Tierärzliche Praxis 1993, *21*, 87-94.

Sahni YP & DN Srivastava: Analgesic effect of aspirin modified by cyproheptadine and paracetamol. Indian Vet. J. 1992, *69*, 699-702.

Sawyer DC: Pain control in small-animal patients. Applied Animal Behaviour Science 1998, *59*, 135-146.

Short CE & KA Otto: Preanesthetics and anesthetic adjuncts. In: Lumb & Jones' Veterinary Anesthesia, Thurmon JC, Tranquilli WJ and Benson GJ (eds), 3rd ed., Williams & Wilkins, Baltimore, 1996, 183-209.

Wallace J, J Sanford, MW Smith & KV Spencer: The assessment and control of the severity of scientific procedures on laboratory animals. Laboratory Animals 1990, *24*, 97-130.

Walter T, TT Chau & BM Weichman: Effects of analgesics on bradykinin-induced writhing in mice presensitized with PGE_2. Agents and Actions 1989, *27*, 375-377.

Wilhelmi G: Species differences in susceptibility to the gastro-ulcerogenic action of anti-inflammatory agents. Pharmacology 1974, *11*, 220-230.

Wixson SK: Anaesthesia and analgesia. In: The biology of the laboratory rabbit, ed 2, Manning PJ, DH Ringler DH & CE Newcomer (eds.). New York, Academic Press, 1994, pp 87-109.

Wixson SK & KL Smiler: Anesthesia and analgesia in rodents. In: Anesthesia and analgesia in laboratory animals. Kohn DF, Wixson SK. White WJ, and Benson GJ (eds). Academic Press, New York, 1997, pp 165-203.

Wright EM, KL Marcella & JF Woodson: Animal pain: Evaluation and control. Lab. Animal. 1985,*14*,20–36.