Tierärztliche Vereinigung für Tierschutz

GV-SOLAS
Gesellschaft für Versuchstierkunde

Expert Information

Committee on Anaesthesia of GV-SOLAS
Supported by The working group 4 of TVT
(German veterinary association for animal welfare)

Pain management for laboratory animals

Status: May 2015

This current recommendation is an up-to-date version of the first recommendation of the Committee on Anaesthesia of GV-SOLAS issued in 2002. It was reviewed and revised in 2015 by the Committee on Anaesthesia of GV-SOLAS:

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This recommendation is intended for licence applicants, animal welfare officers, and authorities. Its purpose is to support work practices that maintain animal welfare standards. Pain relief methods are constantly evolving (e.g. new analgesics, application methods and intervals, dosages). It is everyone’s responsibility to be informed about current standards and most re-cent developments in pain treatment for laboratory animals.

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Contents

1 Pain, suffering, harm

By establishing the terms pain, suffering, and harm in its Animal Welfare Act, German law defines the relevance of animal welfare for handling animals and performing surgical procedures on them. (§1 TSchG; „No one may cause an animal pain, suffering or harm without good reason.“)

Pain

The term „pain“ is distinguished from experience that describes psychosocial impacts on individuals, like stress, distress, suffering, and harm. Focusing on the physiological sensory aspect of pain is reasonable from a practical point of view and yet restricting when it comes to comprehending pain in its entirety.

The definition of pain given by the International Association for the Study of Pain (IASP 1994, Jensen 2008) illustrates this as well: Pain is „an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or de-scribed in terms of such damage“. A further explanatory note states: „Pain is always subjective!“

A human investigator can never fully comprehend this unpleasant sensory and emotional experience. He can only grasp an animal’s pain according to his own scope of experience.

Suffering

Suffering is a mental state based on the failure to meet an individual‘s basic needs. (Gärtner 2002).

Due to the varying needs of different species and individuals a universal definition of suffering cannot be given. From a legal point of view, the degree and extent of suffering are certainly an issue, and so is time:

On the one hand, the term „suffering“ does not call for a prolonged or lasting impairment of well-being. On the other hand, it implies a relevant condition; based on that, suffering means more than plain discomfort, listlessness or a mere temporary state of exposure. (BGH, German Federal Court of Justice, 1987). It is also important to note that: Suffering can be addressed as a subjective sensation. It can further be a consequence of pain. (Hackbarth and Lückert 2000) Like pain, suffering can only be assessed through one’s own personal experience or personal view.

Harm

Harm experienced by individuals is linked to pain and suffering, with time being a decisive factor. It seems to be the case when an animal’s condition is changed for the worse. Harm can be a cause, side effect or consequence of pain and suffering. However, pain and suffering can also precede, accompany or succeed harm. (Schiwy 1998, Hackbarth and Lückert 2000)

For animals, painless harm and suffering is also relevant. And from an animal welfare point of view, analgesic therapy covers only part of the exposure laboratory animals are subjected to.

2 Development of pain

Pain stimuli are transmitted from the point of origination to the spinal cord via myelinated A delta fibres and unmyelinated C fibres. The fast-conducting myelinated fibres transmit impulses that convey primary pain that is easy to localize. Primary pain leads to avoidance and a motoric response that works as a means of protection. The slow-conducting C fibres transmit impulses that convey dull, burning pain that is difficult to localize. This kind of pain which can be long-lasting, even if the initial stimulus has stopped, is also called secondary pain.

A noxa or trauma usually causes an inflammatory reaction, thus initiating a pathological process in the affected tissue. This process is accompanied by a release of mediators (e.g. prostaglandins, histamine, bradykinin, leukotrienes, nitrogen monoxide and other cytokines, among others) that sensitize nociceptors. The consequence is primary hyperalgesia and elevated pain sensitivity, based on a lower sensitivity threshold for damaging stimuli induced pain. This cause of pain can be increased time-dependently by changes in sensory transmission in the peripheral and central nervous system. Such processes are described as allodynia (alteration of pain threshold: non-painful stimuli are experienced as painful), wind-up phenomenon, and pain memory. They characterize secondary hyperalgesia (expansion of elevated pain sensitivity to adjacent, non-traumatized areas).

The outline below is meant to help understand not only the development of pain but also the effect of pain relief management:

Nociception means transformation of a stimulus into electrical activity at the peripheral nociceptor (transduction) and transmission of nerve impulses. A modulation of impulse transmission can occur in the central nervous system, starting in the spinal cord. After transduction, transmission, and modulation it is the perception that presents the actual conscious, subjective, and emotional experience of pain. That is what is commonly understood as “pain”.

3 Recognition and quantification of pain

In 1987, Jenkins stated that animal pain was often difficult to recognize. This is still true today, even though the aspect of animal pain has become more relevant in laboratory animal science. As implied in the statement above, animal pain, like human pain, must be interpreted from a subjective point of view (Haskins 1992, Van Hooff et al. 1995, Flecknell 1996). The close resemblance of the nociceptive system of an animal to that of a human being (Gebhart 1994, Van Hooff et al. 1995, Flecknell 1996) leads to the assumption that an animal, regardless of its age or species, feels postoperative pain (Erhardt 1992, Pascoe 1992, Henke et al. 1999).

Based on this assumption, the difficulty of pain recognition becomes an issue of pain quantification and a question of identifying the degree and extent of pain that makes pain prophylaxis and pain management necessary and adequate.

The German Animal Welfare Act distinguishes between „pain“ and „substantial pain“. According to the legislation of the German Animal Welfare Act (TierSchG) and the Experimental Animals Ordinance (TierSchVersV), as well as the articles of the Directive 2010/63/EU it is required that when applying for a project licence an investigator needs to assess the pain a laboratory animal is likely to feel in the course of the project and also that occurring pain is reduced to a minimum with adequate pain management (§5 (1) TierSchG, §7 (1) 1a TierSchG, §8 (4) TierSchG, §17 (1) TierSchVersV, Art. 14 (4) Directive 2010/63/EU). This is, in many respects, a call for action to quantify animal pain.

4 Why pain relief? (Pathophysiological aspects)

For German law, the relevance of pain management in laboratory animals is evident from §1[1] and §7a, (2) 4[2] of the German Animal Welfare Act. These sections suggest that any animal experiment that is accompanied by postoperative or other pain requires adequate pain management.

[1] No one may cause an animal pain, suffering or harm without good reason.
[2] Pain, suffering, or harm may be inflicted on the animals only when unavoidable to attain the purpose of the experiment. They may not be inflicted, particularly, for work, time or cost saving reasons.

Moreover, pain has a pathophysiological effect that affects experimental results in a non-controllable way, more than analgesics do. Highly intense and long-lasting pain can even result in death.

Below is an exemplary list of pathophysiological effects of pain on the various organ systems of a body (Jage 1997, Larsen 1998, Henke and Erhardt 2001).

Endocrine system

- Secretion increase: catecholamines, corticoids, glucagon, growth hormone, ACTH, ADH
- Secretion decrease: insulin, testosterone
- Effect: impaired mobilization, languor, amyotrophy, prolonged convalescence
- Fluid retention, oliguria, electrolyte disorder
- High metabolic rate with increased oxygen consumption
- Effects on the organ systems which see

Neuroendocrine system

- Beta-endorphin level increase
- Blocking of NMDA channels

Sympathetic nervous system

- Increase in activity, release of catecholamines
- Effects of a prolonged stimulation of the sympathetic nervous system:
  - Decreased tissue circulation with increasing tissue acidosis which leads to pain amplification
  - Risk of hypoxia in organs with poor circulation (heart, brain, colon, lungs)
  - Gastrointestinal atony to the point of a paralytic ileus
  - Activation of the renin-angiotensin system with poor renal perfusion,
  - thus increasing peripheral vasoconstriction
  - Increased thrombocyte aggregation
  - Increased release of noradrenaline in peripheral nerve endings and thus induced pain amplification

Immune system

- Immunodeficiency (increased susceptibility to infections), impaired wound healing
- Immunosuppressions
  - Inhibition of the mitotic rate and locomotion of T cells
  - Inhibition of lymphokine production
  - Inhibition of phagocytosis
- Decreased
  - Interleukin release
  - Cell immunity

- Tumor immunity
- Host defense status
- Generation of antibodies

Changes in blood count

- Depletion of spleen and skin vessels
- Lymphopenia
- Eosinopenia
- Neutrophilia

Respiratory system

- Particularly affected after thoracic and abdominal surgery
- Reduced tidal volume and vital capacity, tachypnoea
- Effect: Atelectases with impaired pulmonary gas exchange, thereby
- Promotion of infections, pneumoniae
- Respiratory and metabolic acidosis

Cardiovascular system

Effects are caused by activation of the sympathetic adrenergic system.

- Tachycardia, peripheral vasoconstriction with increased blood vessel resistance
- Increased heart contractility with increased myocardial O2 consumption
- Increase in blood pressure

Gastrointestinal system

Cause:

- Stimulation of peritoneal nociceptors, increased activity of the sympathetic nervous system, ischemia

Effect:

- Gastrointestinal atony to the point of a paralytic ileus with nausea, vomiting, colon distension and increased abdominal pressure
- Elevated diaphragm with restrictive pulmonary function
- Irritation of visceral nociceptors
- Impaired visceral circulation with ischemia, thereby increased pain symptoms
- Reduced food and water intake (hypoglycemia, dehydration)

Genitourinary system

- Reduced motility in the entire urinary tract
- Urinary retention

Musculature

- Spasms, tremor, cramps
- Prolonged: impaired mobilization, languor, amyotrophy

Behaviour

- Depression, increased aggressive behaviour, automutilation
- Reduced grooming activity (particularly rodents)

Behavioural changes and abnormalities in animals are important indicators for assessing the degree of animal pain. And yet it can be difficult to objectify and interpret behavioural deviations, especially in small laboratory animals.

5 Effects of analgesics on animal test results

A basic principle is:

When there is reason to believe that an animal is in pain or its pain is actually perceptible, it is imperative to administer analgesics. It is also imperative during and after painful surgery.

German law, however, acknowledges that there are certain cases that need to be justified when applying for a project licence, where pain relief treatment is not possible as it may compromise the purpose of the project (TschG §5 (4) 1 and TierSchVersV §17 (3)).

If applicants cannot verify this, they are advised to proceed as follows: In addition to the non-treated project test group, another group is included in the experiment that is treated with analgesics. If there is no significant difference in parameters between these two groups, analgesics are to be used for similar projects in the future. Effects of analgesics must be verified in vivo, not just in vitro (including cell culture).

The results of this „special study“ should be communicated to the licensing authority and, if possible, be published in a scientific journal on laboratory animal testing.

They might help promote the licensing of future projects and at the same time pro-vide a deeper understanding of animal care in experiments in accordance with animal welfare regulations.

The following points both summarize findings in the relevant literature and describe the authors’ experience concerning the effects of analgesics on organ functions. At present, they are primarily individual observations and are not intended to be exhaustive. Any additions and corrections are welcome and will be considered for further issues of this paper.

The species in which the effects were observed are underlined.

5.1 Blood parameter

5.1.1 Haematology (Blood cells)

Erythrocyte count, leukocyte count, hemoglobin content, hematocrit

Immediate effects of analgesics, administered on a short-term basis, are rarely observed. There are, however, reports on rare occurrences of agranulocytoses in humans, with antipyretics like *metamizole* and *paracetamol*. (Mayer 1997) Compared to control groups, rats show no significant changes in blood cell count and function with administration of *meloxicam*, tolfenamic *acid, ketoprofen*, *buprenorphine* (Pitschi 2001), *metamizole*, *flunixin meglumine*, and *carprofen* (Fürst 2000).

Tepoxalin, given in doses 1 to 6 times higher than the therapeutic dosis, leads to a decrease in hemoglobin content and hematocrit and to an increase in leukocyte count. Therapeutic doses cause no changes in rats and dogs. (Knight et al. 1996)

Thrombocytes

Several non-opioids cause more or less distinct inhibition of platelet aggregation.

Acetylsalicylic acid (ASA) is probably one of the most effective aggregation inhibitors. In most mammals, this inhibition is irreversible and causes changes in blood clotting until all thrombocyte cells are renewed (8 to14 days post appl.). In sheep, however, ASA is no aggregation inhibitor. Depending on the administered dose, it leads to an increased platelet aggregation. (Spanos 1993)

In humans, *ketoprofen* causes inhibition of thrombocyte aggregation for 36 hours (Gandini et al. 1983, Niemi et al. 1999). With acute administration, no extension of PTT is discernible. A

subacute administration, however, leads to a longer bleeding time. Even when combined with warfarin, it does not influence the prothrombin time; there is no change in clotting cascade parameters. There is also no change in clot-ting time from a clinical point of view. (Mieszczak and Winther 1993)

In rats and dogs, *tepoxalin* tends to increase the thrombocyte count. (Knight et al. 1996)

In humans, the local anaesthetics *bupivacaine* and *lidocaine* cause significant clotting lags (thromboelastogram), both having a lag increasing effect when administered in equianalgesic doses. (Tobias et al. 1999)

5.1.2 Clinical chemistry (Blood levels)

Enzymes, urea, creatinine, total protein, bilirubin, AST (aspartate aminotransferase), ALT (alanine aminotransferase), AP (alkaline phosphatase), GLDH (glutamate lactate dehydrogenase), γ GT (γ glutamyl transpeptidase):

In cats, *carprofen* and *ASA* do not induce any changes. (Parton et al. 2000) In rats, *meloxicam, tolfenamic acid, ketoprofen* and *buprenorphine* (Pitschi 2001) as well as *metamizole*, *flunixin meglumine* and *carprofen* (Fürst 2000) have no influence on blood levels, either. In humans, *buprenorphine* has a prolactin-increasing effect (Mendelson et al. 1989).

In calves, *meclofenamic acid* has a plasma protein-lowering effect. (Booth and McDonald 1988)

5.2 Immunological approaches

5.2.1 Anaesthetics and opioids

Fentanyl and *buprenorphine* suppress the LPS-induced increase of TNF α in mouse serum in the endotoxemia model (Endotoxinämiemodell), meaning they have an anti-inflammatory effect. This effect is dose-dependent (Piersma et al. 1999). According to Lysle et al. (1993) and Nelson et al. (1997), opioids suppress the mitogen-stimulated proliferation of T and B cells in rats; they lower NK cell activity and IFNγ and interleukin 2 production as well as the primary antibody response (Lockwood et al. 1994); macrophage phagocytosis capacity is reduced (Tubaro et al. 1983, Fecho et al. 1994) and LPS induced TNFα production diminished (Bencsics et al. 1997). The mechanisms at work are not well known. They affect the CNS (hypothalamic pituitary adrenal axis) and, through opiate receptors, immunocompetent cells (μ3 receptors on macrophages and monocytes) that block the inhibition of IL 1 and TNFα induced chemotaxis (Makman 1994).

Byshovets et al. (1997) observe no immunosuppression caused by *butorphanol* like it is caused by pure opiates in humans.

Administration of *fentanyl* and *pethidine* in vitro selectively suppresses IL 4 production and generalized macrophage-induced cytokine production. When administered in high doses, the cytolytic activity of T cells is suppressed, as well. B cell proliferation and NK activity are less inhibited. As naloxon has no neutralising effect these impacts are not transmitted through opiate receptors (House et al. 1995).

Studies in immunotoxicity of *buprenorphine* in rats (Van Loveren et al. 1994): Over 4 weeks 0,1 to 1,6 mg/kg/d s.c., with high doses less gain in BW, less liver weight, less glycogen storage, more fatty vacuolation, slight gain in relative lung weight in the lowest dosage group, dose-dependent increase in interstitial pneumonia, gain in adrenal glands weight in the two highest dosage groups, no haematological and bone marrow changes. Gain in thymus weight, gain in popliteal and mesenteric lymph node weight, no changes in splenic weight; immunoglobulin A concentration is significantly lower in the highest dosage group; IgG increased.

Administration of morphine in C57BL/6 mice has a two phase effect on immunological parameters. The macrophage-induced inhibition of tumor cell proliferation is stimulated after 20

minutes and blocked after 24 hours. There is no difference in NK activity. *Methadone* does not influence any parameter. (Pacifici et al. 1994) In mice, *dihydroetorphine* reduces dose-dependently gain in BW, splenic weight, thymus weight and the generation of antibody forming cells; lymphocyte proliferation is inhibited and IL 2 production suppressed. Subchronic administration thus means dose-dependent suppression of humoral and cellular immune function. This immunosuppressive effect is more distinct than with morphine. (Wu et al. 1999)

According to Sacerdote et al. (1997), acute administration of *tramadol* in mice leads to immunomodulation which disappears when *tramadol* is applied chronically, with antinociception being maintained. It is thus recommended for patients in which no immunosuppressive effect is desired.

The immunomodulatory and antinociceptive effect of opiates in rats works through several mechanisms. Immunosuppression peaks after 1 hour and has disappeared completely after 24 hours. Antinociception peaks after 30 minutes to 2 hours and is not verifiable after 6 hours. The peak effects thus run more or less parallel. (Nelson et al. 1997)

According to Sacerdote et al. (2000), stress of surgery alone causes a significant depression of lymphoproliferation. There are no changes in NK activity by either surgery or administration of *morphine*. NK activity, however, is significantly increased by *tramadol*. In humans, *tramadol* results in decreased immunosuppression.

Gaveriaux et al. (1998) proof that in mice, the μ receptor is involved in immunosuppression.

5.2.2 NSAIDs

In vitro studies show that *flunixin meglumine* inhibits the leukotriene B4 directed migration of canine polymorphnuclear leukocytes completely after 1 hour and still has significant effects after 24 hours. Part of the anti-inflammatory effect can thus be attributed to the inhibition of these cells. The phenylbutazone-treated reference group is far less affected (Strom und Thomsen 1990).

5.3 Body weight

A *buprenorphine* dose of 0,05 mg/kg in rats causes initial weight loss (Jacobson 2000, Pitschi 2001).

With administration of *carprofen, metamizole, flunixin meglumine, meloxicam, tolfenamic acid,* and *ketoprofen*, rats show similar changes in body weight as the untreated control group. The group treated with 0,3 mg/kg buprenorphine is the only one, contrary to the aforementioned groups, to gain body weight 1 day p.op. and then loose weight up to day 7. After that, this group gains weight continuously, yet always below the levels of the aforementioned groups (Fürst 2000, Pitschi 2001). Mice loose body weight after surgery (laparotomy). But also after anaesthesia (sevoflurane, ketamine/xylazine/acepromazine) and when treated with *buprenorphine* (0,1 mg/kg) and *flunixin meglumine* (5 mg/kg), mice loose body weight without any preceding pain-inducing intervention. Also, with administration of buprenorphine (0,1 mg/kg), feed intake is reduced.

5.4 Behaviour

A multitude of behavioural parameters is suitable for pain detection and for proofing the effectiveness of pain management with analgesics.

A one-time injection of *buprenorphine* (0,05 - 0,3 mg/kg) in rats is sufficient to increase uncontrolled eating behaviour and thus the stomach content significantly. It is induced by the so-called pica behaviour, equivalent to the symptom of vomiting in other species, which involves eating non-nutritious substances, in most cases bedding material (so-called allotriophagy) (Takeda et al. 1993, Clark et al. 1997).

0,3 mg/kg *buprenorphine* (rats), however, cause light sedation with reduced participation in surrounding activity, limited motility, and concurrent hyperacusis. With chronic application, after a 12 hour treatment interval, this dose reproducibly leads to „crepitation sounds“, which would have to be interpreted as gnashing of teeth (Pitschi 2001, Haberkern 2002). Cowan et al. (1977) observe similar behavioural patterns, like stereotypic licking and biting movements, after a one-time application. After acute application of *buprenorphine*, mice show increased physical activity; in rats, stereotypic licking and biting movements occur while guinea pigs show severe depression (Cowan et al. 1977). Minor doses (0,01 - 0,05 mg/kg) lead to increased physical activity in rats (Liles und Flecknell 1992).

In mice, *cocaine* (7,5, 17 and 30 mg/kg i.p.) leads to a significant and dose-dependent increase in locomotion for 1 hour post administration. *Buprenorphine* (0,5 and 5 mg/kg, i.p.) also increases the urge to move for 30 to 60 minutes after the injection. A lower dose has no effect. The cocaine-induced locomotion cannot be modified by a premedication with buprenorphine (Jackson et al. 1993).

With *carprofen* and *ketoprofen*, Roughan and Flecknell (2001) observe no behavioural changes in rats that are solely analgesic-induced.

Compared to a non-treated control group, rats show no behavioural changes during a 30 day treatment with clinically relevant doses of *meloxicam*, *tolfenamic acid*, and *ketoprofen* (Pitschi 2001, Haberkern 2002).

5.5 Wound healing

In rats, the wound healing process is not affected by *meloxicam, tolfenamic acid, flunixin meglumine, ketoprofen, carprofen* and *metamizole*. With *buprenorphine*, the wound stability seems to be slightly reduced at some points. Comparisons in terms of cytological and histological parameters show no significant variance (Fürst 2000, Nätscher 2002, Pitschi 2001, Krahl 2001).

Adspection of skin wounds shows no difference in scab formation between rats that have been treated with *meloxicam*, *tolfenamic acid*, *ketoprofen, carprofen, metamizole* and *buprenorphine* and their control group (Fürst 1999, Nätscher 2002, Pitschi 2001, Krahl 2001).

In the first 7 days p.op., *meloxicam*, *tolfenamic acid* and *ketoprofen* increase wound strength while during the same time, according to the relevant literature, *flunixin meglumine* reduces the tensile strength of wounds. After this 7 day period, *meloxicam* and *ketoprofen* seem to have a continuing positive effect on wound strength (DONNER et al. 1986, Pitschi 2001, Haberkern 2002).

There are clinical reports on wound healing impairment after cruciate ligament surgery in dogs caused by analgesia with *meloxicam* (Grosse et al. 1999). Another publication, however, issued by the same house did not verify those reports (Tatari 2001).

It is not ultimately clear whether infiltrating a wound with local anaesthetics slows down the healing process. A one-time application is not likely to affect the process, especially in rodents whose wounds heal fast. Dermal application for days or weeks seems to affect and slow down wound healing (Brower u. Johnson 2003).

5.6 Bone healing

(see also dissertations Geiger 2002, Haberkern 2002):

In rats, in vitro applications of *NSAIDs* have a negative effect on osteoblast growth (Herr et al. 1990).

While analgesic treatment in rats does affect single periods of growth, it has no effect on the overall result. The most distinct healing tendency can be observed with *buprenorphine* and

meloxicam after day 10; with *metamizole* and *flunixin meglumine*, the process tends to start later. With *carprofen*, the healing process is unaffected at any time. On day 30 at the latest, all groups show the same reparation as the control group.

General condition is least affected by *flunixin meglumine*; distinct bone healing, however, is observed only after day 20. *Metamizole* impairs bone healing for 30 days. After that, the *metamizole*-treated group shows the same healing as the control group. Animals often show a reduced general condition. This is also the case with administration of *meloxicam*. Bone healing yet starts very early, with a healing process equivalent to that of the control group. In the first three days, general condition is least affected by *buprenorphine*, and bone healing starts early (Geiger 2002).

For examinations in the early healing stage, it is recommended to use *tramadol* (Krischack et al. 2007).

5.7 Colon healing

Analgesic effects on colon wound healing have rarely been studied. Schnitzler et al. (1992) did studies in pigs, comparing the effects of *morphine* and epidural analgesia with *bupivacaine* on the tensile strength of the anastomosis and on the hydroxyproline content of wound areas. No significant differences to the untreated control group were observed.

What is generally observed is opioid-induced slow colon motility, resulting from spasmogenic activity. *Pethidine* seems to be an exception among opioids, having a spasmolytic effect on the GI tract in all animal species, the same way as *metamizole* has (Flecknell and Waterman-Pearson 2000, Henke and Erhardt 2001).

According to Hirschowitz (1994), all *NSAID*s share more or less strong side effects in the gastrointestinal mucosa. He advises against the application of NSAIDs for treating gastrointestinal diseases. In humans, wound healing in peptic ulcers is slowed down (Tobias et al. 1999).

In rats, colon healing is inhibited due to immobilisation valence and spasmogenic activity of most *opioids* (Jurna 1998).

For colon resection in rats, *oxymorphone* is preferable to *buprenorphine* (Gillingham et al. 2001).

Administration of *morphine* or *buprenorphine* following colorectal resection in pigs had no significant effect on blood flow, bursting pressure or hydroxyproline content. In both groups, however, the colon transit time was increased (Schnitzler et al. 1992).

5.8 Angiogenesis/Vascular proliferation

COX-2 selective and non-selective *NSAIDs* inhibit angiogenesis in vitro in rat endothelial cells by directly affecting those cells, e.g. by blocking of ERK2 kinase activity and translocation of ERK2 in the nucleus (Jones et al. 1999).

In mice, *morphine* increases leukocyte-endothelial interactions by stimulating the NO production. This effect can be neutralised by naloxon (Ni et al. 2000).

5.9 Specific experimental approaches

5.9.1 Arthritis

In rats with inflammatory pain, *morphine* modulates the thermal and mechanical antinociception on a peripheral and central level. Although *morphines* have peripheral points of application the application route does not affect arthritic progression (Bürkle et al. 1999).

In chronic pain models in rats (adjuvant arthritis), the analgesic potency of chronic *morphine* administration can be tested (Cain et al. 1997).

In chronic arthritis models in rats, in vitro administration of *buprenorphine* inhibits osteoclastic bone resorption. In vivo, it has a pro-inflammatory effect with increased joint destruction. Suffering is reduced. The interpretation of results, however, becomes more difficult (Hall et al. 1996).

Buprenorphine has an anti-inflammatory effect in rats and seems to modulate the destructive joint phase (Volker et al. 2000).

In rats with adjuvant arthritis, *metamizole* reduces hyperalgesia and oedema, dose-dependently, although it has a better analgesic than anti-inflammatory effect. It works through mechanisms that do not include a release of PG-like substances (Tatsuo et al. 1994).

In rats, *meloxicam* reduces the arthritis-induced peripherally transmitted reflexive responses (swelling, stiffness, hyperalgesia, pain behaviour) without affecting the centrally transmitted reflexes. The speed of this process is indicative of the direct effect on the sensitised nociceptor (Laird et al. 1997).

Meloxicam is effective in dogs with induced arthritis (Van Bree et al. 1994). In birds, an intra-articular injection of *bupivacaine* stops musculoskeletal pain (Hocking et al. 1997).

In rats, transcutaneous electrical nerve stimulation *(TENS)* can prevent hyperalgesia alltogether. Low doses of naloxon (selective μ inhibitor) block anti-hyperalgesia of low frequency TENS; high doses of naloxon (μ, δ, κ inhibitor) block high frequency TENS. High TENS is effective through delta receptors in the spinal cord, low TENS through μ receptors. Blocking the κ receptor is without effect (Sluka et al. 1999).

5.9.2 Endotoxic shock/Sepsis

In rats with E. coli sepsis, naloxon + *buprenorphine* and naloxon + epinephrine improve the MAP, BE, and pH level. *Buprenorphine* is thus an alternative therapy for endotoxic shock treatment (Tseng und Tso 1993).

In dogs with E. coli sepsis, *flunixin meglumine* stops hypotension, hypoxaemia, and the early stage of portal hypertension. It also lowers the number of lung bacteria (Hardie et al. 1987).

In dogs with experimentally induced endotoxemia, administration of subanaesthetic doses of ketamine has an immunomodulating effect, particularly on TNF alpha plasma concentration (DeClue et al. 2008).

5.9.3 Examinations in pregnant animals

In dogs, *flunixin meglumine* causes only partial inhibition of prostaglandin synthesis and is without effect on the birth process (Williams et al. 1999).

5.9.4 Ischaemia and reperfusion

Brain

Rats with cerebral ischaemia are less prone to infarction with administration of (+)-pentazocine than (-)-pentazocine (Takahashi et al. 1997). *Fentanyl* enlarges ischaemic lesions in rats (Kofke et al. 1999). In humans with increased intracranial pressure, *alfentanil*, *sufentanil* and *fentanyl* induce a transient increase in intracranial pressure, but there is no proof of cerebral ischaemia caused by those substances (Albanese et al. 1999).

Tail

Reperfusion hyperalgesia in rats is inhibited by *metamizole*. Nociception, however, is not either by *metamizole* or *indomethacin*, *diclofenac*, *paracetamol* or *ibuprofen* (Gelgor et al. 92a). *NSAIDs* have no effect on flight behaviour. Also with intracerebroventricular administration,

reperfusion hyperalgesia in rats is inhibited, which points to the production of prostanoids in the CNS (Gelgor et al. 1992b).

Hindlimbs

With ischaemia of hindlimbs and multiple organ dysfunction syndrome (MODS) in mice, *buprenorphine* ensures adequate analgesia without affecting the measured parameters (Wiersma et al. 1997).

Heart

In dogs, premedication with *butorphanol* increases the threshold for ischaemic preconditioning and thus for inducing cardiac protection (Schwartz et al. 1997).

Eye

Flupirtine is a neuroprotective agent against retinal ischaemia as it affects the ATP level. *Flupirtine* can lower NMDA receptor activity in rabbits (Osborne et al. 1996).

Stomach

If *acetaminophen* is administered in rats before gastric ischaemia by clamping the A. coeliaca, the erosion area will be diminished and lipid peroxide increase inhibited, as well as in vitro lipid peroxidation. *Acetaminophen* thus protects the gastric mucosa against ischaemia reperfusion damage (Nakamoto et al. 1997).

Kidney

In the renal ischaemia model, mice with *buprenorphine* treatment show a quicker recovery, less weight loss and a better regulation of body temperature. The degree of kidney damage after ischaemia and reperfusion seems to be unaffected (Deng et al. 2000).

Small intestine

In rats, a premedication with *morphines* imitates protection by preconditioning. Premedication thus stimulates endogenous opioids like leuenkephalin (Zhang et al. 2001).

5.9.5 Liver function

In patients (human) with reduced liver function (e.g. cirrhosis), *metamizole* has a longer kidney-independent elimination half life (Zylber-Katz et al. 1995).

5.9.6 Gastrointestinal tract motility

Buprenorphine administration in rats (0,01 - 1,0 mg/kg s.c.) results in slow colonic transit time. A dose of over 1 mg/kg leads to a transit time equivalent to that of the control group animals (Cowan et al. 1977). *Oxymorphone* produces no change in colon motility. Antinociception measurements with colorectal distension are not affected (Briggs et al. 1995).

5.9.7 Neuropathy

A chronically intermittent *morphine* administration in rats can prevent neuropathic pain from developing. It does not result in tolerance to *morphine* (Chu et al. 2000).

In rats with peripheral neuropathy, low doses of *ketamine* (0,01 - 1,0 mg/kg) can attenuate nociception (mechanical allodynia + hyperalgesia, cold allodynia, spontaneous pain) without any side effects (Qian et al. 1996).

5.9.8 Kidney function

Human patients with a creatinine clearance of less than 30 ml/min require less follow-up doses of *butorphanol* (Shyu et al. 1996).

In humans, *diclofenac* causes a massive decrease in ureteral peristalsis (urogram). These changes are not so much expressed in limited perfusion as in reduced diuresis. With *pethidine*, no such changes are observed (Brough et al.1998). After receiving postoperative treatment with *ketorolac*, *ketoprofen* or *morphine* for 1 to 2 days, healthy dogs showed a significant decrease in Na clearance and a decrease in specific urine weight. In addition, some of the animals treated with *ketorolac* and *ketoprofen* showed a transient azotaemia. Kidney function is least affected by *carprofen* (Lobetti und Joubert 2000).

5.9.9 Peritonitis

I.p. injection of *morphine* in mice stops inflammations by reducing (directly and indirectly) the content of plasmatic chemotactic factors (lower peritoneal leukocyte count, compensation by means of high activity). (Chadzinska et al. 1999)

5.9.10 Visceral pain

In rats, a mechanical, visceral pain can be produced repeatedly and reversibly by stretching the duodenal lumen. Pain reponse can be prevented dose-dependently by administering *morphine* (Colburn et al. 1989).

A human study showed that visceral pain, caused by dilation of the distal oesophagus, can be reduced significantly by administering *ketamine* (Strigo et al. 2005).

In rats, local μ and δ *opiate* receptors can modulate the spinal visceral nociceptive transmission. κ Receptors cannot. (Danzebrink et al. 1995)

Colorectal distension is an effective model for verifying opioid-induced visceral antinociception in rats (Briggs et al. 1995).

In rats with colon inflammation, κ opioid receptor agonists show great potency, which is indicative of a peripheral upregulation of κ receptors. In the colorectal distension model, morphine and κ opioid receptor agonists inhibit the visceromotor response in inflamed and non-inflamed colons (Sengupta et al. 1999).

5.9.11 Postoperative pain

Subcutaneous and intrathecale *morphine* administration increases the pain response threshold in rats (Zahn et al. 1997).

5.9.12 Tumor occurrence

Menke and Vaupel (1998) tested several anaesthetics and analgesics for their effect on tumor blood flow in rats. Thiobarbiturate, chloral hydrate and methoxyflurane have a slightly increasing effect, etomidate, *ketamine* x*ylazine*, *fentanyl* fluanisone and urethane a slightly decreasing one. Midazolam, midazolam + *ketamine*, *fentanyl* + droperidol, droperidol, diazepam and pentobarbital cause no changes in blood flow compared to that in non-anaesthetised animals. There are no time-dependent changes. Only urethane and methoxyflurane cause a slight increase in blood flow over time and a slight decrease in vascular resistance.

Morphines induce apoptosis and inhibit TNFα gene expression. Some opioids can affect the growth of human tumor cell lines (antitumor activity) (Sueoka et al. 1998).

Tilidine shows no tumorigenic potential in rats and mice (McGuire et al. 1986).

If, in rats, the pain suppression system is activated directly by a non-opioid subsystem (direct cerebral injection of *β endorphin*), the artificial lung metastasis count can be increased. This system is to be blocked by naloxon (Simon et al. 1984). In mice, various opiates can inhibit as well as stimulate the growth of sarcoma 37 and its dissemination. They can also reduce the growth-stimulating effect of surgical trauma (Beliaev et al. 1985).

In vitro pretreatment with *pentazocine* has a growth-inhibiting effect on tumor cells (Ehrlich ascites cells) in mice. I.p. injection of *pentazocine* in mice, in addition to the tumor cell injection, has a life-prolonging effect (Kigoshi et al. 1981).

The B16BL6 melanoma in mice causes pain and hyperalgesia which increase after day 14. *Morphine* inhibits hyperalgesia. In phase 2, however, higher doses are required which soon lead to a *morphine* tolerance. *Morphine* administered in this manner suppresses tumor growth and metastasis. A neurectomy in the tumor area has the same effect (Kuraishi et al. 2001).

A heroin pretreatment one week prior to an S20Y cell (neuroblastoma) injection in mice inhibits tumor growth and has a life-prolonging effect; it is effective in all doses. There is no difference in tumor size compared to control groups. This effect can be blocked by naloxon. *Opiates* thus have a modulating effect on neoplasia growth (Zagon und McLaughlin 1981).

6 Pain suppression in and around surgery

6.1 General anaesthesia

Premedication – Preemptive analgesia

Premedication in general means administration of a sedative and/or analgesic and/or an anticholinergic agent prior to anesthesia.

A premedication with □2 adrene
profound sedation of 3 to 6 hours, accompanied by minor analgesia (xylazine: 5-10 min, medetomidine: 30-45 min).

This premedication can also be done as a sedative analgesic premedication, which comes close to the concept of preemptive analgesia. This concept means administration of analgesics like opioids (e.g. fentanyl, levomethadone, buprenorphine, butorphanol) or phencyclidine (ketamine) to prevent secondary hyperalgesia from developing before any pain occurs. Lower postoperative doses of analgesics are required. A minimal dose of ketamine in particular seems to inhibit this sensitization. Ketamine has a particularly favourable effect on ischaemic and somatic pain. A dosage of 0,1 to 0,2 mg/kg administered in the p.op. phase is effective for approximately 30 min. Ketamine shows synergism with opioids (Lascelles 2000). This dos-age stops postoperative hyperalgesia for 10 -12 hours (Slingsby 1999).

The effectiveness of a preoperative administration of buprenorphine in small rodents is often difficult to assess, which involves a risk of misinterpreting the depth of anesthesia and of increasing respiratory depression during anesthesia. There-fore, only experienced anaesthetists should use buprenorphine preemptively. All others are advised to an intra- and postoperative administration. Moreover, opioids, and buprenorphine in particular, cause a specific Behaviour in rats, the so-called pica Behaviour, which shows their discomfort and leads to undesired allotriophagy.

This preemptive analgesia can also be achieved by neuroleptic analgesia (NLA): Premedication with a neuroleptic (e.g. acepromazine, azaperone) and analgesic (e.g. fentanyl, levomethadon, buprenorphine, butorphanol) leads to a neuroleptic analgesic state that combines deep sedation with profound analgesia.

Surgical anaesthesia

It should be considered that part of the pharmaceutical drugs used for anaesthesia induce no analgesia. The most widely used pharmaceutical drugs with no primary analgesic effect are: benzodiazepine (e.g. diazepam, midazolam), neuroleptics (e.g. acepromazine, azaperone), propofol, barbiturates (e.g. thiobarbiturates, pentobarbi-tal), isoflurane, and sevoflurane.

These pharmaceutical drugs can be used for painful surgery:

- if it involves only a brief pain stimulus,
- if the induced hypnosis is deep enough (however, stronger side effects are to be expected).

The following methods are suitable premedication for more painful surgery:

- Hypnoanalgesia

  = Hypnotic (e.g. propofol) + analgesic (e.g. fentanyl, ketamine)

  applicable for all animal species; the prototype of heart-protecting anaesthesia, the depth of anaesthesia can be altered at any time, recommended as continuous drip with perfusors
- Sedative (e.g. xylazine, medetomidine) + analgesic (e.g. ketamine)

The combination of xylazine and ketamine is frequently used for anaesthesia in laboratory animals. This combined anaesthesia can further be stabilised by substitution of acepromazine.

- Inhalational anaesthesia
  - As mono-anaesthesia in rodents (no intraoperative reaction to pain stimuli); it is necessary though for an adequate preoperative analgesic to reach its effective level in due time prior to a fast wash-out; buprenorphine, for example, must be administered at least 30 min prior to surgery.
  - Surgical tolerance achieved through mono-anaesthesia causes low blood pressure due to cardiotoxicity resulting from high doses of inhalational an-aesthesia. As it is well controllable mono-anaesthesia is often used in small laboratory animals.
  - As combination to injection anaesthesia to form a balanced anaesthesia; especially in animal species that allow i.v. application of anaesthetics. Inhalational anaesthetic as well as injection anaesthetics can be administered in a balanced way. In dogs, it is possible to combine i.v. basal anaesthesia with further i.v. anaesthesia and, in low doses, with isoflurane.

Analgesia in the course of anaesthesia

Stage I of anaesthesia (stage of analgesia in human medicine):

- Induction stage with gradual reduction of consciousness
- Is equivalent to sedation with neuroleptics (e.g. acepromazine, azaperone); consciousness of individuals is to a greater or lesser extent reduced; spontaneous motor activity is reduced; voluntary reactions continue.
- Painful manipulation results in defensive movements and expressions of pain and leads to an increase in catecholamine; it is not subject to amnesia. Thus painful manipulation should not be carried out without additional systemic or regional administration of analgesics.
- No actual analgesia!

Stage II of anaesthesia (stage of excitement)

- Occurs with every start and finish of anaesthesia.
- Induced by high i.v. doses of benzodiazepines, □2-agonists, neurolept
  inhalation of anaesthetics through inhalation masks or inhalation chambers.
- Stress or pain stimuli appear to increase symptoms of excitement. Possible countermeasure: immediate i.v. injection of propofol (3-5mg/kgBW) to deepen anaesthesia.
- Neuroleptanalgesia can cause hyperacusis.
- No actual analgesia!

Stage III$_1$ of anaesthesia (stage of hypnosis)

- Induced by anaesthetics with hypnotic effect (e.g. propofol, barbiturates with/without premedication with benzodiazepines, □2-agonists) or by neuro
  inhalational anaesthetics (e.g. isoflurane, sevoflurane).
- In case of mono-anaesthesia with inhalational anaesthetics: Deepening to stage III2 can only be achieved with a concentration level that impairs circulation.

- Unconsciousness with good muscular relaxation[3] but no analgesia, unless substances with analgesic effect have been administered.
- Pain stimuli lead to a higher heart and respiratory rate and to raised blood pressure due to a release of catecholamines; they can also lead to uncoordinated movements.
- Prolonged pain can cause a neurogenic shock with all consequences of circulatory failure even during anaesthesia.
- If in doubt, administration of a short-acting analgesic is recommended (e.g. fentanyl, alfentanil, remifentanil) or administration of an analgesic that is al-so effective after anaesthesia, like levomethadone, piritramide or pethidine.
- A hypnotic in low doses (propofol, thiobarbiturate) or inhalational anaesthetic leads to the ideal stage of surgically useful anaesthesia, to stage III2 of anaesthesia.

Stage III_2 of anaesthesia (stage of surgical tolerance):

- This stage by definition leads to pronounced analgesia.
- If pronounced analgesia is induced by means of mono-anaesthesia with inhalational anaesthetics, it can reach toxic levels.
- It is recommended to use combined anaesthesia to reach that stage, e.g. basal anaesthesia with injection anaesthetics prior to inhalational anaesthesia, or an adequate combination of different injection anaesthetics.

Stage III_3 of anaesthesia (stage of depression):

- Most reflexes are eliminated.
- Respiration and circulation are strongly depressed.
- All pain reactions are suppressed.

Stage IV of anaesthesia (stage of asphyxia):

- All reflexes are absent; pupils are dilated and show no light reflex.
- Spontaneous respiration: respiratory arrest and severe circulatory depression.
- No apparent reaction to pain stimuli!

Conclusion about analgesia during anaesthesia

Up to a depth of anaesthesia equivalent to stage III1 analgesia is not active. There-fore, if pain is expected, additional analgesic measures have to be taken. Administration of nitrous oxide is not sensible. Different than in humans, it has no analgesic effect in animals. It has, however, potentiating effect on other anaesthetics.

[3] If muscular relaxants are added for anaesthesia, the animal will not be able to react to pain stimuli with muscular contractions (movements, reflexes). It is therefore absolutely necessary to monitor the respiratory and circulatory response to pain stimuli in order to assess the depth of anaesthesia and ensure adequate pain suppression. Using muscular relaxants for the sole purpose of immobilisation during painful procedures compromises animal welfare.

Stages of anaesthesia in different species

Stage	Name	Analgesia	Rodent	Rabbit	Dog	Cat	Pig	Sheep
I	Analgesia	-	Reduced consciousness, spontaneous motor activity diminished, no amnesia					
II	Excitement	-	Rowing motion, trembling whiskers, urine output	Opisthotonus, nystagmus, nibbling, urine output	Head shaking sideways, uncontrolled snapping poss., yawning, tongue rolling, nystagmus	Opisthotonus, extensor spasms, hissing	Rowing motion	Trembling, nystagmus, uncontrolled head movements
III_1	Hypnosis	-	Muscular relaxation, pedal reflex mild +, palpebral reflex +/-, respiratory and circulatory reaction to pain stimuli					
			Central eyeball position		Mild prolapse of nictitating membrane, eyeball rotation, swallowing reflex frequent +		Eyeball rotation	Salivation
III_2	Surgical tolerance	+	Pedal reflex straight -, palpebral reflex -, ear pinching reflex -, corneal reflex +, no reaction to pain stimuli					
			Mild exophthalmos	Mild eyeball rotation, mild prolapse of nictitating membrane	Eyeball rotation, severe prolapse of nictitating membrane		Trunk pinching reflex -, central eyeball poisition	Salivation
III_3	Depression	+	Pedal reflex --, corneal reflex -					
			Severe exophthalmos	Fish eye, fixed eyeball, severe prolapse of nictitating membrane	Central eyeball position			Salivation stops
IV	Asphyxia	++	No reflexes, gasping, pupils are dilated and fixed, central eyeball position, dry cornea, dry mucous membranes					

6.2 Local analgesia

Types of local analgesia (also local anaesthesia):

- Surface analgesia: Skin, cornea, mucous membranes (all species)
- Infiltration analgesia: Conduction anaesthesia, plexus block (rats and larger)
- Epidural analgesia: Epidural puncture and instillation of local anaesthetics, morphine or α_2 agonists

The following substances are used as local anaesthetics:

- Procaine, tetracaine, lidocaine, mepivacaine, bupivacaine, ropivacaine, etidocaine, oxybuprocaine, proxymetacaine

Application of local analgesia as well as measures taken under local analgesia only, mean considerable stress for animals. Therefore, local anaesthesia should almost never be given without basal anaesthesia.

6.3 Systemic analgesics (for postoperative care)

The following systemically active analgesics are appropriate for postoperative care:

1. Opioids
   - Buprenorphine, piritramide, pethidine, butorphanol, tramadol, fentanyl
2. Non-opioids

2.1. Non-steroidal antiphlogistics (NSAIDs)
   - Carprofen, etodolac, flunixin meglumine, ketoprofen, meclofenamic acid, meloxicam, niflumic acid, phenylbutazone, piroxicam, tepoxalin, tolfenamic acid, vedaprofen

2.2. Antipyretics
   - Metamizole, acetylsalicylic acid

3. Phencyclidine
   - Ketamine as pre- or intraoperative bolus with peri- and postoperative continuous drip infusion

Substances for pain treatment that are often indiscriminately used in human medicine (diclofenac, paracetamol ...) should be avoided for various reasons (often toxic, too short half-life...).

Types of application

Intravenous

Intravenous injections are a safe type of application ensuring a quick onset of action (exception: delayed onset of action with buprenorphine). They are most appropriate for administration of opioids. A peripheral catheter can be used for continuous application (continuous drip infusion, perfusor) which is also a sensible means of administering short-active analgesics. This type of application is not common for small laboratory animals.

Intramuscular

Intramuscular injections are painful and should be avoided, particularly in small animals. In pigs, however, intramuscular injections are easier to make and thus preferable over subcutaneous applications.

Subcutaneous

Subcutaneous injections are most common for immediate postoperative care. They are well appropriate for NSAIDs due to their high bioavailability after subcutaneous application. If opioids are applied subcutaneously, higher doses are required due to a reduced resorption as when applied in other ways. A very elegant approach to postoperative pain management is the use of osmotic mini-pumps, implanted subcutaneously, for a continuous release of analgesic.

Percutaneous

Percutaneous applications of analgesics involve the use of patches available with fentanyl and buprenorphine. This type of application should only be used after careful consideration due to its special characteristics:

- These patches are designed for humans and are not well adaptable to the body weight of animals, small animals in particular. It is difficult to find the appropriate dosage.
- Pain symptoms affect skin circulation which can affect skin resorption and lower the effect levels of analgesics.
- Onset of action and effectiveness of analgesics can differ considerably in different individuals.
- If applied at an early stage (preemptively), they might increase respiratory depression induced by application of general anaesthetics.

Oral

Oral applications are not appropriate for immediate postoperative care, unless analgesics are applied directly into the oral cavity (drops). A sufficient oral intake of analgesics with feed or water cannot be ensured due to a pain-induced reduction of feed and water intake after surgery. As oral administration is generally stress-free for animals, it can be useful though to continue with this type of application after an initial parenteral application.

Local application

Local anaesthetics can be used in addition to a parenteral therapy. Examples are:

- local infiltration: costal nerv blocks after thoracotomy
- epidural injection: analgesia after surgery in the posterior half of the body
- intra-articular: application of opioids, as intra-articular localised opioid receptors are verified

The following dosage tables are based on relevant literature and the experience of the authors. Dosages must be adapted individually to the respective clinical situation and experiment. Common side effects can be taken from the product information. The most frequent side effects occurring with routine usage can be taken from the table below. Acute side effects occur primarily after quick intravenous injections.

6.4 Effects and side effects profile for commonly used substances

(Details about dosages can be found in the next section.)

	Agent	Brand name (examples)	Field of application	Contraindications / side effects	Annotations
Opioids	Piritramide	Dipidolor	Most severe pain of all kinds (primarily p.op.)	Long term application (>3d), because of obstipation	Titrating, with tightly monitored breathing activity
	Fentanyl patches	Durogesic	Prolonged analgesia up to 3 days in dog, rabbit, pig, ruminant	Rodents, when instant analgesia is required, fever, respiratory depression	Initial therapeutic gap of 6-24 hours, irregular absorption, thorough patient and user protection (see package insert)
	Tramadol	Tramal	Minor to moderate pain, as continuous drip infusion (CDI) or added to the drinking water of small rodents	Severe pain	Short activity, poss. CDI or added to the drinking water of rat and mouse
	Pethidine	Dolantin	Minor pain; due to spasmolysis adequate for all colon, bile duct and pancreatic duct surgery	Long term application	Short activity
	Buprenorphine	Temgesic	Moderate to severe pain; for part antagonisation of effects of pure μ agonists	Bile duct and pancreatic duct examination, obstipation when administered >5d	In low doses excitatory, in high doses sedating, allotriophagy, Cave when administered preoperatively
	Methadone	Heptadon	Severe pain in dogs, cats	Restlessness during recovery, panting, bradycardia, vocalisation	Active 3-4 hours
	L-Methadone	L-Polamivet			Active 3-4 hours, L-Polamivet contains fenpipramide (parasympatholytic)
	Butorphanol	Morphasol	Short term therapy for moderate to minor pain	Long term treatment, severe pain	excellent antitussive effect
Non-opioids	Acetylsalicylic acid	Aspirin, ASA	Minor inflammatory pain when antithrombotic effect is desired, fever	Risk of bleeding, GI tract dammage	Cave when administered preoperatively risk of bleeding
	Metamizole	Vetalgin, novalgin	Minor to severe pain, abdominal pain primarily, spasmolytic, long term application in CDI only, fever	Long term treatment	Can be well combined with opioids Cave only very slowly i.v.
	Carprofen	Rimadyl	Inflammatory pain of all kinds, surgical pain primarily; also acute and chronic inflammations of the musculoskeletal system	Gastrointestinal and kidney defects	Particularly effective when administered pre-insult, can be applied on a long term basis, can be well combined with opioids
	Flunixin meglumine	Finadyne	Acute and chronic inflammatory pain, endotoxic shock		Certain nephrotoxicity
	Ketoprofen	Romefen	See above, also for eye surgery		
	Meloxicam	Metacam	Pain of all kinds		Particularly effective when administered pre-insult, can be applied on a long term basis, can be well combined with opioids
	Phenyl-butazone	Tomanol, phenylarthrite	Anti-inflammatory, primarily in the musculoskeletal system, poss. for ruminants		Wide range of side effects, not for routine application
	Tolfenamic	Tolfedine	Acute and chronic		Well suitable for cats

	acid		inflammatory pain, antipyretic		
Phency-clidine	Ketamine	Ketasol	Pain of all kinds	Increased muscle tone, hyperthermia, reflexes are maintained	Primarily in combination with opioids, bolus, poss. plus CDI (short activity)

6.5 Useful approaches

Stress of all kinds lowers the threshold for pain. A stress-free environment and stress-free handling, anything that is beneficial for an animal’s well-being, is the best way to reduce the need for analgesics.

The following approaches are useful:

Intraoperative

- Atraumatic surgery: knowing the respective surgical procedures (tissue-conserving surgery, short surgery time, tension-free sutures, few drainages)
- Minimally invasive procedures
- Adequate perioperative monitoring and care (fluid therapy, position, warmth, …)

Postoperative

- Cold packs (particularly for immediate use after tissue trauma)
- Hot packs (for hypothermic animals; but useful after most anaesthetic treatments)
- Keeping the animals in familiar groups and/or familiar surroundings
- Long term sedatives (perphenazine) for animals that are extremely restless, aggressive or autoaggressive (e.g. automutilation in rodents and rabbits)

Supportive therapy

Pharmaceutical drug		Small laboratory animals	Dog, cat	Sheep, pig	Indications (examples)
Perphenazine		Small laboratory animals (in general) 5 mg/kg s.c., active usually for several days (Pachtner 1998) rat Perphenazine enanthate (Decentan-Depot©, Merck, Darmstadt) for intramuscular application, dosage 5 mg/kg BW in 1% solution in medium-chain triglycerides (Miglyol 812©, Caesar & Loretz, Hilden) (total injection volume: 0,2 ml). First intramuscular injection one day preoperative, further injections at an interval of 3 days for a longer period.			Prevention of auto mutilation, phantom limb pains
Scopolamine + metamizole (Buscopan compositum ®)		0,2 - 0,4 ml/animal i.m., s.c.	Cat Do not use for cats. dog one-time 0,1 ml/kg i.v., i.m.	One-time 0,1 ml/kg i.v., i.m.	Gastroenteritis, spastic colic, tympani (ruminant), spasms in the urogenital area
Steroidal antiphlogistics	Prednisolone	Rodent + rabbit 1-2 mg/kg every 24 h i.v., s.c.	Dog 0,5-1 mg/kg every 12-24h, then every 48h i.v., i.m., p.o. cat 2,2 mg/kg every 12-24 h, then every 48 h i.v., i.m., p.o.	Horse, ruminant, pig 0,5 mg/kg i.m.	For inflammatory oedemas Not in combination with NSAIDs
	Dexamethasone	Rodent + rabbit 0,2 mg/kg every 24 h i.v., s.c.	Dog 0,1-0,2 mg/kg every 12-24h i.v., i.m., p.o.; anti-inflammatory anti-allergic: 0.1 - 0.5 mg/kg i.m. or i.v.; cerebral and spinal cord swelling or oedema post trauma/discopathy/tumor: initially 2-3 mg/kg i.v., then taper to 0.2 mg/kg per day cat 0,1-0,2 mg/kg every 12-24h i.v., i.m., p.o.	Horse, ruminant, pig 0,06 mg/kg i.v., i.m.	

7 Dosage tables

7.1 Dosage table dog

Substance	Dose (mg/kg)	Application method	Application interval	Comment
Buprenorphine	0,01 - 0,02	i.v., i.m., s.c.	6 - 8h	The application interval can be prolonged by combining Buprenorphine with other analgesics.
Butorphanol	0,1 - 0,5 - 1,0	i.v., i.m., s.c.	1 - 2h	
Fentanyl patch	5 - 10 kg: 25µg/h, 10 - 20 kg: 50µg/h, 20 - 30 kg: 75µg/h, from 30 kg: 100µg/h	Transdermal	48 - 72h	Cave oral intake
Methadone L-methadone	0,1 - 0,5	s.c., i.m., i.v.	4h	Panting, restlessness
Pethidine	2,0 - 6,0	i.m., s.c.	1 - 2h	Spasmolytic in smooth muscles
Piritramide	0,1 0,2 0,1 (- 0,3)/h	i.v. s.c. i.v.	1 - 2h 2h CDI	
Tramadol	1 (- 3)/h	i.v.	CDI	
ASA	25,0 10,0	p.o. slowly i.v.	6 - 8h	
Metamizole	20,0 - 50,0	slowly i.v., s.c., i.m.	4h	Spasmolytic in smooth muscles
Carprofen	4,0 or 2,0	i.v., i.m., p.o., s.c.	24h 12h	
Flunixin meglumine	0,5 - 1,0	i.v., i.m., s.c., p.o.	24h	For 3d max, with endotoxic shock every 12h
Ketoprofen	1,0 - 2,0 from 2.d 0,5 - 1,0	i.v., i.m., s.c. p.o.	24h	For 3 - 5d
Meloxicam	0,2	p.o., s.c., i.v.	24h	After first application dose to be reduced to 0,1 mg/kg
Piroxicam	0,3	p.o.	48h	
Tolfenamic acid	4,0	s.c., p.o.	24h	3d max
Ketamine	As bolus for pain management 0,5-2 mg/kg (e.g. before surgery, during anaesthesia); as continuous drip infusion during anaesthesia 10-30 µg/kg min^{-1} for postoperative pain management 2-20	As bolus i.m., i.v. as continuous drip infusion		Continuous drip infusion, to be titrated down gradually (e.g. after 18 h only 2 µg/kg min^{-1})

	µg/kg min^{-1}			

7.2 Dosage table cat

Substance	Dose (mg/kg)	Application method	Application interval	Comment
Buprenorphine	0,005 - 0,01	i.m., s.c., i.v.	8 - 12h	Mydriasis, hyperthermia
Butorphanol	0,1 - 0,5	i.v., s.c., i.m.	2 - 4h	
Pethidine	5,0 - 10,0	i.m., s.c.	2 - 3h	
ASA	10 - 25	p.o.	24 - 36h	
Metamizole	20 - 50	slowly i.v., i.m., s.c.	6h	Churn!!
Carprofen	2,0 - 4,0	i.v., i.m., p.o., s.c.	24h 12h	
Flunixin meglumine	0,125 - 0,25	s.c.	12h	For 3d max
Ketoprofen	1,0 - 2,0 initially, 0,5 - 1,0	s.c., p.o. p.o.	24h	For 3 - 5d
Meloxicam	0,2 initially, then 0,1	s.c., p.o.	24h	
Tolfenamic acid	4,0	s.c., p.o.	24h	3d max
Ketamine	As bolus for pain management 0,5-2 mg/kg (e.g. before surgery, during anaesthesia) as continuous drip infusion during anaesthesia 10-30 µg/kg min^{-1} for postoperative pain management 2-20 µg/kg min^{-1}	As bolus i.m., i.v. as continuous drip infusion		Continuous drip infusion, to be titrated down gradually (e.g. after 18 h only 2 µg/kg min-1)

7.3 Dosage table rabbit

Substance	Dose (mg/kg)	Application method	Application interval	Comment
Buprenorphine	0,01 - 0,05	s.c., i.m., i.v.	8 - 12h	
Butorphanol	0,5	s.c.	4 - 6h	
Metamizole	20,0 - 50,0	slowly i.v., i.m., s.c.	4h	
Carprofen	4 - 5	i.v., s.c., p.o.	24h	
Meloxicam	0,2 - 1,0	s.c., p.o.	12h	

7.4 Dosage table rat

Substance	Dose (mg/kg)	Application method	Application interval	Comment
Buprenorphine	0,03 - 0,05	s.c.	6 - 12h	
Butorphanol	0,5 - 2,0	s.c.	4 h	

Substance	Dose (mg/kg)	Application method	Application interval	Comment
Tramadol	0,5 mg/mL in drinking water	p.o.	Continuously	In drinking water. Regular water consumption must be assured (frequent drinking, sufficient volume).
ASA	100	p.o.	24h	
Metamizole	100	s.c., p.o.	6h	
Carprofen	4,0 - 5,0	s.c.	24h	
Flunixin meglumine	1,0	s.c.	24h	
Meloxicam	0,2-1,0	s.c., p.o.	24h	

7.5 Dosage table guinea pig, chinchilla, mouse, hamster

Substance	Dose (mg/kg)	Application method	Application interval	Comment
Buprenorphine	0,05 - 0,5 (guinea pig)	s.c., i.p.	6 - 12h	Not hamster
	0,05 - 0,1 (mouse)			
Butorphanol	1,0 - 5,0	s.c.	4 - 6h	Not hamster
Tramadol	1 mg/mL in drinking water (mouse)	p.o.	Continuously	In drinking water. Regular water consumption must be assured (frequent drinking, sufficient volume).
Flunixin meglumine	3,0 - 5,0 (mouse)	s.c.	12h	
ASA	120,0 - 300,0	p.o.	24h	Not hamster, guinea pig
Metamizole	80,0 (3 drops/kg) (guinea pig)	p.o.	Every 4 - 6h	
	200,0 (8 drops/kg) (mouse)			
	100,0 (4 drops/kg) (hamster)			
Carprofen	4,0 - 5,0	s.c.	12 - 24h	
Meloxicam	0,5 (guinea pig) 1 (hamster/mouse)	s.c., p.o.	12 - 24h	

7.6 Dosage table horse, ruminant and pig

(dose information in mg/kg BW)

Substance	Horse	Ruminant	Pig
Buprenorphine	0,004 - 0,006 i.v., i.m.	0,001 - 0,01 i.v., i.m., s.c. every 6 - 12h	0,005 - 0,05 - 0,1 i.v., i.m. every 8 - 12h
Butorphanol	0,05 - 0,1 i.v., i.m. every 8h	0,2 - 0,5 i.m., s.c. every 2 - 3h	0,1 - 0,3 i.m. every 4h
Morphine	0,05 - 0,1 i.v., i.m. every 4h, up to 0,25 max	0,2 - 0,5 i.m. every 2h	0,1 - 1,0 i.m. every 4h, up to 20 mg max
Pentazocine			1,5 - 3,0 i.m., i.v. every 4h
Pethidine	1,0 - 2,0 i.m. every 1 - 2h	2,0 i.m., i.v. every 2h	2,0 i.m., i.v., up to 1,0g/animal max, every 2h
Piritramide		0,1 - 0,5 i.v., every 2 - 6h	0,1 - 0,5 i.v., s.c. every 2 - 3h
Acetylsalicylic acid	25,0 p.o. every 12h 2x, then 10,0 every 24h	50,0 - 100,0 p.o. every 6 - 12h	10,0 p.o. every 4 - 6h
Metamizole	25,0 slowly i.v. every 12h	25,0 - 50,0 i.v., i.m. every 6h	25,0 - 50,0 i.v., i.m., p.o. every 6h
Carprofen	4,0 i.v., p.o. every 24h	4,0 i.v., s.c. every 24h	4,0 i.m., p.o., i.v., every 24h
Flunixin meglumine	1,1 i.v., s.c., p.o. every 24h, 5d max	2,2 i.v. very 24h, 5d max	1,0 - 2,0 s.c., i.v. every 24h
Ketoprofen	1,1 - 2,0 i.m., i.v. every 24h, for 3-5d	3,0 i.m., i.v. 3d max	3,0 i.m., 1x
Meclofenamic acid	2,2 p.o. every 24h, an 5-7d		
Meloxicam	0,6 i.v. every 24h, 14 days maximum (oral application possible)	0,5 s.c., i.v. every 24h, 3d max	0,4 i.m. every 24h
Phenylbutazone	4,5 p.o., every 24h, 4g/animal/day max	10-20 initially p.o., then 2,5-5,0 p.o. every 24h	10 p.o. every 12h
Tolfenamic acid		2,0 i.m. every 24h	
Vedaprofen	1,0 - 2,0 p.o. initial dose, followed by 1,0 after 12h, for 14d max		

7.7 Dosage table birds

Substance	Dose (mg/kg)	Application method	Application interval	Comment
Buprenorphine	0,25 - 0,5	i.m.	6h	
Butorphanol	1,0 - 4,0	i.m	2h	
Metamizole	25 (1 drop/kg)	p.o.	6h	Empirical
Carprofen	4,0 - 6,0	i.m., s.c.	12 - 24h	Empirical
Meloxicam	0,1 - 0,5	s.c., p.o.	24h	

8 Recommendations on analgesic procedures

8.1 Head

Viscerocranium

Tissue / organ	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Oral cavity	mainly oral	stomatitis, gingivitis surgery in the dental apparatus jaw bone: implants, partial resections	dog minor, cat moderate to severe minor, pulpitis moderate minor, if sufficient stability is achieved; moderate to severe, if the Nervus alveolaris is damaged suffering and harm due to reduced food intake	3 - 5 days	dog pig	antiphlogistics (steroidal and non-steroidal) Irritation of cranial nerves often requires additional opioids.
Jaw joint	several	implants, resections	depending on chewing load, myofascial syndrome of the masticatory muscles, symptoms with convergence to other structures in the distribution of the Nervus trigeminus moderate to severe suffering and harm due to reduced food intake	3 - 5 days	dog pig	NSAIDs poss. muscle relaxation required occasional need for additional opioids
Nose, paranasal sinuses, sinuses		tumor formation	similar to headaches minor to moderate		mouse rat	metamizole, NSAIDs
Eye, eye socket		all ophthalmological models	irritation of the cornea or the Nervus opticus, raised intraocular pressure extremely painful	3 - 5 days	all	antiphlogistics (steroidal and non-steroidal) cornea local poss. glaucoma therapy opioids when needed

Tissue / organ	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Inner ear, middle ear		bulla osteotomy blast injury	very pain-sensitive structures (Nervus facialis, Nervus trigeminus)	3 - 5 days none	all	NSAIDs mainly with opioids
External auditory meatus			No analgesia only with extremely short exposure!	1 - 2		NSAIDs
Horn		amputations	well innervated	1 - 3 days	sheep	long-acting, regional anaesthesia, NSAIDs

Neurocranium

Tissue / organ	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Neurocranium	trepanation boreholes	stereotactic surgery	access and irritation p.op. painful (instability of implants, infections)	1 - 3 days p.op.	all	Local anaesthetic, opioids in combination with steroidal antiphlogistics
		probe implantation	Periosteum and meninges are very sensitive to pain!			
	minimal trepanation	inoculations of tissue, cells or infectious substances	directly p.op. minor	0 - 1 day	mouse rat	if minor: metamizole NSAIDs
		tumor implantation	increase in intracranial pressure painful (tumor growth, oedema), pain radiation to facial and cervical region (Sprotte 1993)	Space-occupying lesions require continuous therapy.		oedema treatment (mannitol infusion)
			Epileptiform seizures can increase suffering!	Termination condition!		anticonvulsives, sedatives
		global brain trauma	increase in intracranial pressure painful	3 days	mouse rat	oedema treatment (mannitol infusion) metamizole NSAIDs

8.2 Musculoskeletal system

Spine

Tissue / organ	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Nerve root also spinal disc	dorsolateral dorsal ventral[4]	exp. radiculitis, stenosis surgery and exp. inflammations or degeneration of spinal discs irritations possible after any spine surgery	radicular pain: often distally radiating, sensory disturbance, often sharp and pulling pain, expressions of pain cervical spine: pain in head, neck and shoulder area due to projection (Kerr, 1961) autonomic malregulations poss., symptom dysfunction pain severe to moderate, motion-dependent	2 - 3 days	all	antiphlogistics (steroidal and non-steroidal) oedema treatment (mannitol infusion) poss. muscle relaxation required occasional need for additional opioids
Small vertebral joints end plates of vertebral bodies also spinal disc	dorsal dorsolateral dorsolateral ventral[4]	implants, stiffening spinal disc surgery all changes in biomechanical integrity of the spinal cord (Kirkaldy-Willis, 1988, Mooney, 1987)	non-radicular pain: dull, deep-seated, difficult to localise spasm of the deep paravertebral muscles (Bogduk, 1983) moderate to severe	3 - 5 days	all	NSAIDs poss. muscle relaxation required occasional need for additional opioids

Extremities

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Bones	several	fracture models stable unstable	 minor moderate	 2-3 days long term treatment	all	NSAIDs, opioids as needed

[4] Laparoscopic, thoracoscopic: additional exposure see laparoscopy, thoracoscopy

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Muscle, fascia	several	access to the skeletal system arthrotomy trauma models[5]	myofascial pain: dysfunction and local algesia, also distant radiation of pain autonomic faulty regulation possible moderate to severe	3 - 5 days	all	NSAIDs, metamizole (short acting) muscle relexation required occasional need for additional opioids
Nerve	several	access to the skeletal system arthrotomy trauma models[5]	radicular pain: segmental distribution, altered pain, temperature and surface sensibility intra-articular trigger point: often no rest pain moderate to severe	1 - 3 days	all	NSAIDs muscle relaxation as needed occasional need for additional opioids
Vessel (see blood vessel table)	several	extensive ischaemia	ischaemic, vascular pain up to severe pain	continuous (long term treatment)	all	opioids in combination with NSAIDs
Joint	several	orthopaedic models	often myogenic and arthrogenic pain (osteopathic lesion) moderate	1 - 3 days	all	antiphlogistics (mainly non-steroidal) rest (husbandry, bandage technique) muscle relaxation as needed occasional need for opioids (initial), combination with NSAIDs recommended
Paw toe end organ		injections (virus suspension, LCMC, vaccinia) immunisation[5] burn chemical burn[5] contusion[5]	often distinctly painful Verify models!	5 days minimum	mouse rat	Avoid! opioids in combination with NSAIDs, metamizole

[5] Antiphlogistic therapy and experimental model are often uncombinable, therefore particularly painful.

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Amputations			phantom pain to 25% remaining amputation stump pain acute p.op., also to 60% chronic: osteitis, callus and scar formation, vascular, neuroapathic (% information for humans) (Loeser, 1990; Stermann et al., 1980, 1984) extremely painful	prophylactic treatment as soon as possible, preoperative at least 10 days	all	regional anaesthesia, long term opioid therapy calcitonin in 1-3 days up to 5x 0,1mg/kg p.o. 3-4 doses per day Perphenazine (Decentan^{R}) for 3-5 days

Musculoskeletal system

Pain due to neoplasia

Tissue damage (Strumpf 1993)	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
tumor growth: - bone and soft part infiltration - compression and infiltration of nerve, blood and lymph vessels, - oedema with impaired circulation - tumor necrosis of the skin, ulceration and secondary infection therapy induced: radio therapy: - fibrosis, neuropathy, - radiation osteomyelitis, chemotherapy: - inflammation, - neuropathy	tumor models	inconsistent: bone and periosteal pain, soft part pain, radicular pain, function failure and irritation tumor-induced 60-90%, treatment-induced ca. 5% of pain exposure (Twycross, Fairfield, 1982) 37% painful even at an early stage (human)! pain prevalence: (Zech et al., 1988,Bonica, 1985) 60% soft part tumors, 75-80% bone tumors often profound (Bonica, 1990)	long term treatment	mouse rat	antiphlogistics steroidal and non-steroidal, metamizole, in later stages additional opioids required Use local anaesthesia! Termination condition!

8.3 Respiratory tract

Lung

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
partial resection	thoracotomy		profound (thoracotomy)	3 - 8 days	all	local anaesthesia (e.g. bupivacaine intercostal) + opioid + NSAIDs and/or metamizole, both as needed
transplantation	thoracotomy		profound (thoracotomy) in case of transplant failure	4 - 8 days longer according to symptoms Define termination condition!	rat pig dog	local anaesthesia (e.g. bupivacaine intercostal) **+** opioid + NSAIDs and/or metamizole I, both as needed
ventilation			none		all	only anaesthetised animals or profoundly sedated animals (analgosedation: opioid/NSAIDs)
pneumonia			none		all	
pneumonia/ pleurisy			very painful	whole duration of experiment	rabbit	NSAIDs

Trachea

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
		stent implantation	12-24h			NSAIDs

8.4 Cardiovascular System

Heart surgery

Model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Heart surgery with open thorax (chronic open-chest models)	lateral thoracotomy	myocardial infarction caused by complete or partial occlusion of coronary vessels (ligature, ameroid constrictors) stenosis of large vessels (aorta pulmonaris, aorta) testing of surgical techniques, substances or implants (surgical robots, laser devices, cardiac valve replacement) surgery for chronic instrumentation for intrathoracic measurements (telemetry electrodes on the heart, indwelling catheter) gene therapy experiments	severe exposure to pain for 1 to 2 days analgesia absolutely necessary	3 - 7 days, depending on clinical results	pig dog sheep calf rabbit rat mouse	opioids NSAIDs, metamizole conduction anaesthesia of intercostal nerves recommended (e.g. bupivacaine intercostal)

Model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
	median thoracotomy, sternotomy	myocardial infarction caused by complete or partial occlusion of coronary vessels (ligature, ameroid constrictors) stenosis of large vessels (aorta pulmonaris, aorta) testing of surgical techniques, devices, materials, substances or implants (surgical robots, laser devices, cardiac valve replacement) surgery for chronic instrumentation for heart function measurements (telemetry sender, indwelling catheter) gene therapy experiments	Severe exposure to pain for 5 to 7 days, followed by prolonged moderate or minor pain analgesia absolutely necessary Sternotomy is not recommended for chronic experiments. A reliable stabilisation of the sternum is almost impossible due to thorax shape and natural movements. The natural prone and lateral position of a resting animal leads to prolonged pain and a slow healing process as the severed sternum cannot be stabilised.	until pain symptoms disappear, at least 7 days	dog rat mouse	opioids NSAIDs, metamizole Cave: This model can only be used for special approaches.
Heart surgery without opening the thorax	thoracoscopy	pericardial surgery	minor pain for 1 to 3 days; in exceptional cases (larger tissue lesions) also moderate pain for 1 day	1 - 3 days	dog sheep pig	opioids NSAIDs, metamizole
	A. femoralis, A. carotis	cardiac catheterisation, coronary vessel dilatation with and without substance administration stent implantation, arteriosclerosis induction with catheter, microembolization, myocardial infarction, gene therapy experiments	no pain to minor pain for 1 to 3 days in exceptional cases (larger tissue lesions) also moderate pain for 1 day	0 - 1 days	pig dog rabbit	opioids NSAIDs metamizole one-time application prior to recovery from anaesthesia
Allotransplantation heart / abdomen	donor: thoracotomy recipient: laparotomy	allotransplantation between different rat strains or transgenic mouse strains	donor: no pain treatment necessary recipient: moderate exposure to pain for 3 days due to implantation prolonged pain possible due to secondary reactions, e.g. rejection, thrombosing	3 - 5 days	rat mouse	opioids (buprenorphine recommended) NSAIDs, metamizole

Model	**Access**	**Examples**	**Exposure to pain (degree and duration)**	**Length of analgesic treatment**	**Animal species**	**Proposed treatment**
Induction of pathological changes in the heart due to toxic substances	peroral, parenteral	peroral or parenteral administration of substances that cause pathological changes (inflammation, calcification, micro infarction) in the heart and/or in blood vessels, e.g. inflammatory mediators, antigens, antibiotics, carcinogens, coagulants, detergents, electrolytes	Exposure to pain varies depending on the administered substance and dose: evaluation on account of established data and clinical examination. It may be that the purpose of the project compromises pain treatment.	depending on the clinical course	rabbit rat mouse	opioids NSAIDs, metamizole as needed
Secondary damages of the heart and of blood vessels	several	previous surgery in other organs (kidney, brain) hypertension models genetic modifications inducible transgenic sytems	largely depending on the previous type of modification: evaluation through clinical examination It may be that the purpose of the project compromises pain treatment.	depending on the clinical course	rabbit mouse rat	opioids NSAIDs, metamizole as needed

Blood vessel surgery

Model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Instrumentation in peripheral blood vessels and tissues	A. femoralis, A. carotis, Aorta abdominalis Laparotomy hypoderm, connective tissue muscles	implantation of telemetry systems for taking ECG and/or blood pressure indwelling catheter in peripheral blood vessels	depending on the type of access and the extent of tissue lesion monkey, dog, pig: minor pain for 1 to 3 days; rat: minor to moderate pain for 3 to 5 days; mouse: moderate to severe pain for 3 to 5 days.	mouse, rat: 1 - 3 days monkey, dog pig: 1 - 3 days	rat mouse monkey dog pig	opioids NSAIDs
Occlusion of peripheral blood vessels (see table “Extremities”)	A. femoralis, blood vessel in the ear, A. cerebralis media, A. carotis	ischaemia due to ligature of the A. femoralis or the blood vessels in the ear; cerebral infarction (focal ischaemia) due to cauterisation or catheterisation of the A. cerebralis media; global cerebral ischaemia due to transient occlusion of both carotid arteries	minor to moderate pain for 1 to 3 days; surgery-induced pain only; the brain is not sensitive to pain, focal and global cerebral ischaemia causes no pain.	1 - 3 days	rabbit rat mouse	opioids NSAIDs Cave: In guinea pigs, gerbils, chinchillas as well as some mouse and rat strains, occlusion of the A. carotis or A. femoralis leads to ischaemia in the distribution (mortification of a limb).
Arteriosclerosis or inflammatory peripheral blood vessels	A. carotis, A. femoralis	arteriosclerosis of the A. carotis	minor to moderate pain for 1 to 3 days	1 - 3 days	rabbit rat	opioids NSAIDs A one-time application prior to recovery from anaesthesia is often sufficient.
Transplantation of peripheral blood vessels, implantation of stents and coronary stents	A. carotis, Vena jugularis, Vena cava, Aorta abdominalis	allotransplantation of the A. carotis in different transgenic mouse strains; autotransplantation of blood vessels (artery : vein), prothesis testing in large abdominal vessels	minor to moderate pain for 1 to 3 days	1 - 3 days	mouse rat sheep pig dog	opioids NSAIDs

Growth of peripheral blood vessels	skin	skinfold chamber: transparent chambers integrated in the skin	minor to moderate pain for 1 to 3 days	1 - 3 days post implantation	mouse hamster	opioids NSAIDs

8.5 Digestive tract

Oesophagus

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
		stent implantation	none			
		acidification	none if organs are intact			NSAIDs as needed

Gastrointestinal tract

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Laparotomy	ventromedian in linea alba paramedian paracostal	Sham operation surgery of abdominal organs (pain treatment, which see)	minor to moderate pain for several days slightly less painful for animals than for humans due to other exposure and tension of the abdominal wall	2 - 3 days	all	metamizole opioids (pethidine[6]) NSAIDs
Laparoscopy	several	surgical training, organ retrieval, implantations	minor pain as it requires only minor surgical incisions	1 - 2 days	pig sheep	metamizole NSAIDs
Peritoneum		peritonitis models (vessel ligatures, caecum/colon occlusion with perforation)	moderate to severe pain Irritation of peritoneal nociceptors leads to further symptoms like nausea,vomiting, and low gastrointestinal activity. These symptoms,	until symptoms disappear	all	metamizole opioids (pethidine[6])

[6] Pethidine with its spasmolytic properties is well suited for treating gastrointestinal pain.

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
		extension due to positional change or growth of organ tumours	following colon distension and ischaemia of the colon wall, increase in intra-abdominal pressure, irritation of visceral nociceptors and visceral sympathetic reflexes, can increase pain and atony.			metamizole opioids (Pethidine[6])
		inflammations p.op.				NSAIDs metamizole
Abdomen	ventromedian or paramedian laparotomy	gastric resection (total/partial) gastric fistula (hypodermic needle, port) pouches (Heidenhain, Pavlov) stomach ulcers pyloroplasty rumen fistula (ruminants)	minor to moderate pain for 2 to 3 days resulting from laparatomy stomach pain due to severe distension; extension due to positional changes in the peritoneum or inflammatory changes, possibly prolonged Inflammatory pain can be caused by bacterial infections, ischaemic conditions, released mediators.	2 - 3 days in case of complications until symptoms disappear	rat pig sheep dog mouse	metamizole opioids (Pethidine[6])
Colon	ventromedian or paramedian laparotomy	pouch, fistula (e.g. duodenum: excretory pancreas function), artificial anus, colon resection, colon transplantation, mucosa transplantation, intestinal bypass, ballon expansion colon (colic model), ileus models	minor to moderate pain for 2 to 3 days resulting from laparatomy Severe pain is caused by colic symptoms due to spasmodic muscular contractions or severe colon distension, commensurate with the symptoms. There can also be pain-induced vegetative symptoms (vomiting, colon atony).	2 - 3 days in case of colics until symptoms disappear	rat rabbit pig dog	NSAIDs in combination with metamizole or buscopan comp. in case of severe pain opioids (pethidine[6]) CAVE! colon atony

Liver

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Hepatectomy	laparotomy		minor to moderate pain (laparotomy)	2 - 3 days	all	metamizole NSAIDs
Transplantation (recipient)	laparotomy	orthotopic, heterotopic autogeneic, syngeneic allogeneic, xenogeneic	minor to moderate pain (laparotomy) severe in case of transplant failure	2 - 3 days, longer according to symptoms Identify termination criteria!	rat pig dog	metamizole NSAIDs opioid as needed
Tumor implantation	laparotomy	tumor cells/pieces implanted in the liver	minor to moderate pain (laparotomy) Depending on the type of tumor growth, pain can be severe.	2 - 3 days, longer according to symptoms Identify termination criteria!	mouse rat	metamizole NSAIDs opioid as needed
Liver necrosis, liver cirrhosis, acute liver failure			no pain to severe pain severe pain in the final stage due to inflammation and/or metabolic derangement	according to symptoms Identify termination criteria!	mouse rat rabbit pig dog	metamizole NSAIDs opioid as needed
	laparotomy	<u>Inducted by:</u> occlusion of blood vessels - partial - complete	minor to moderate pain (laparotomy) up to severe pain	2 - 3 days longer according to symptoms	rat pig	metamizole NSAIDs opioid as needed
		bile duct ligation[7]	moderate pain (laparotomy, adaptation processes in the early phase of stasis)	3 - 5 days longer according to symptoms	rat mouse	metamizole NSAIDs opioid as needed

[7] Ligation of the gallbladder duct causes an increased concentration of bile acids in the liver (cholestasis), which leads to biliary fibrosis within 4 - 8 weeks and finally to cirrhosis of the liver. This generally is the aim of the intervention. Looking at the clinical course of progression in humans, we have no evidence of any pain although the ensuing ichtiness of the skin can be perceived as unpleasant. Recommendation: Due to the (mini-) laparotomy, mice as well as rats ought to receive pain relief on a routine basis for 3 - 5 days post-operative. A more prolonged administration is deemed unnecessary and may well be even counterproductive, since most NSAIDs could interfere in the pathophysiology being investigated.

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
	injection iv, ip	hepatotoxins e.g. d galactosamine	no pain to severe pain	according to symptoms	rat	metamizole NSAIDs opioid as needed
	oral, injection ip	administration of carbon tetrachloride	initially none to severe	according to symptoms	rat	metamizole NSAIDs opioid as needed
Liver cirrhosis, liver necrosis	diet	"high-fat - low choline - low protein"	initially none to severe	according to symptoms	rat rabbit	metamizole NSAIDs opioid as needed
Hepatitis	without		usually asymptomatic	according to symptoms	mouse	NSAIDs
Liver biopsy	percutaneous		none		all	
Gallbladder	laparotomy	cholecystectomy	minor to moderate pain (laparotomy)	2 - 3 days	mouse pig dog	metamizole NSAIDs opioid as needed
Bile duct	laparotomy	cannulization for gall extraction	minor to moderate pain (laparotomy)	2 - 3 days	all	metamizole NSAIDs opioid as needed
Gallstones	without	attempts at treatment (**EKS**, laser, ether)	asymptomatic if there is no - inflammation or - bile duct obstruction: then possibly severe pain	according to symptoms	pig	metamizole NSAIDs opioid as needed

Pancreas

Tissue / organ / model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Pancreatectomy	laparotomy	complete/partial	minor to moderate pain (laparotomy)	2 - 3 days	rat pig dog	metamizole NSAIDs opioid as needed
Transplantation (recipient)	laparotomy		minor to moderate pain (laparotomy) severe in case of transplant failure	2 - 3 days, longer according to symptoms Identify termination criteria!	mouse rat pig dog	metamizole NSAIDs opioid as needed
Ductus pancreaticus	laparotomy	cannulization for extracting pancreas secretion	minor to moderate pain (laparotomy)	2 -3 days	rat pig dog	metamizole NSAIDs
Tumor implantation	laparotomy	implantation of tumor cells/pieces	minor to moderate pain (laparotomy) Depending on the type of tumor growth, pain can be severe	2 - 3 days, longer according to symptoms Identify termination criteria!	mouse rat	metamizole NSAIDs opioid as needed
Pancreatitis acute, necrotising	laparotomy	injection of Na taurocholate retrograde in the D. chole-docho pancreaticus, occlusion of the D. choledocho pancreaticus, duodenal stenosis	severe pain severe course of disease	entire project duration Identify termination criteria!	rat	opioid metamizole

Pancreatitis oedematous, reversible	injection ip, sc	caerulein 1X caerulein repeatedly	no pain to minor pain mild course of disease up to severe pain	 according to symptoms entire project duration	mouse mouse	not necessary opioid

Spleen

Tissue/ organ / model	**Access**	**Examples**	**Exposure to pain (degree and duration)**	**Length of analgesic treatment**	**Animal species**	**Proposed treatment**
	laparotomy	splenectomy	minor to moderate pain (laparotomy)	1 - 3 days	all	NSAIDs metamizole
Immunisation	laparotomy	injection under the splenic capsule, implantation of foil with antigens under the splenic capsule	minor to moderate pain (laparotomy)	1 - 3 days	mouse rabbit	NSAIDs

8.6 Genitourinary tract

Urinary tract

Tissue/ organ/model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Laparotomy	Ventromedian in Linea alba, flank for retroperitoneal access	Sham operation	minor to moderate pain for several days slightly less painful for animals than for humans due to other exposure and tension of the abdominal wall	2 - 3 days	all	Metamizole NSAIDs opioids
Kidney	ventromedian, if needed retroperitoneal (bilateral surgery) flank (unilateral)	nephrectomy (total, subtotal, unilateral, bilateral), transplantation, hydronephrosis model implantation of tissue under the kidney capsule	minor to moderate pain Pain is caused by capsular tension due to swelling of the kidneys (pain receptors in organ capsule). A gradual stretching of the capsule causes only minor pain due to receptor adaptation.	with no complications, at least 3 days	mouse rat pig dog	opioids (pethidine) metamizole NSAIDs (Cave! kidney function)
Bladder	ventromedian	bladder resection (total/partial) augmentation	minor pain moderate to severe pain in case of leakage and peritonitis	with no complications, at least 3 days or else until symptoms disappear (particularly with cystitis)	rat rabbit pig	NSAIDs (Piroxicam) buscopan, metamizole pethidine epidural analgesia piroxicam
		models for voiding dysfunction (hyperreflexia - mustard oil; areflexia - flaccid bladder paralysis, Lapides - contracted bladder)	minor to severe pain depending on the model and on postoperative complications			
		inflammation models (instillation of mustard oil)	moderate to severe pain depending on mustard oil concentration (induction of severe hemorrhagic cystitis if concentration is too high)	until symptoms disappear		

Tissue/ organ/model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Ureter	ventromedian, if needed retroperitoneal (bilateral surgery) flank (unilateral)	stent ureteral occlusion (total/partial) for hydronephrosis or reflux nephropathy models	minor pain with slow developing hydronephrosis moderate to severe pain with fast developing stasis caused by colicky pain due to a sudden stretching of the ureter	depending on postoperative course, at least 3 days	rat rabbit pig	NSAIDs (minor pain) opioids (severe pain) primarily Pethidine spasmolytics (busc. comp.) metamizole epidural analgesia (EDA)
Urethra	perianal, ventromedian	urethrostomy (perianal, ventromedian) catheterisation	moderate pain (epithelium)	until symptoms disappear	pig dog	NSAIDs buscopan comp., metamizole

Genital tract

Tissue/ organ/model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Ovary	ventromedian, dorsoventral	ovariectomy (e.g. osteoporosis models) tumor implantation	minor to moderate pain pain due to extension of the peritoneum	with no complications, 2 to 3 days Pain due to tumour growth requires prolonged treatment.	rat guinea pig dog sheep	metamizole NSAIDs opioids
Uterus	ventromedian, flank	foetal operations	great risk of abortion, is increased by use of abdominal press due to postoperative pain	at least 3 days	rabbit pig sheep	opioids In addition to pain treatment, a uterus relaxant is required
Prostate	ventromedian, if need be pelvic osteotomy	prostatectomy	moderate to severe pain depending on the type of access Pelvic osteotomy should only be performed in exceptional cases as it is very painful and often followed by postoperative complications	2 to 3 days Pelvic osteotomy requires a minimum treatment of 5 days.		opioids and NSAIDs epidural analgesiea low-fibre nutrition (space food)
Testicles	scrotal	orchiectomy	minor increased pain due to postoperative swelling	1 day, if there is no complication and no severe swelling	all	NSAIDs

Exterior genital (labia, scrotum)			moderate to severe pain as this region is full of nociceptors; increased pain due to postoperative swelling	until symptoms disappear		NSAIDs (detumescence effect)

8.7 Skin

Skin

Model	**Access**	**Examples**	**Exposure to pain (degree and duration)**	**Length of analgesic treatment**	**Animal species**	**Proposed treatment**
Allotransplantation of tissue in the skin or subcutaneous tissue	skin, subcutaneous tissue	implantation of mouse heart in the subcutaneous tissue; transplantation of skin (human) on immunodeficient mice; allotransplantation of e.g. tracheal tissue in the subcutaneous tissue	minor to moderate pain The extent of pain depends very much on the tension of the skin and on the postoperative inflammatory course.	at least 1 day, Postoperative problems or severe tension require prolonged treatment.	mouse rat	NSAIDs ketamine
Tumor implantation	skin, subcutaneous tissue	injection of tumor cells in/under the skin	minor pain following the injection; more severe pain due to tumour growth and tumor growth-induced tension of the skin	when symptoms appear	mouse rat	opioids Define termination condition!
Burn	skin	surface wounds	Extent of pain depends on the size of the lesion; induction of allodynia and hyperpathia with large lesions; particularly severe pain during manipulations (bandage changing); short-acting general anaesthesia may be sensible	depending on the extent of pain, longer period possible		opioids ketamine NSAIDs
Wound healing	skin	simple incision	minor	several hours to 3 days depending on the extent of the trauma		NSAIDs metamizole

Tattooing	skin	ear tagging	short term moderate pain	one-time	rabbit (ear) dog cat primates	metamizole preemptively, and/or locally with cream (Emla cream); is no substitute for general anaesthesia that may be required by law (animal welfare act)

8.8 Surgery involving reproduction techniques, genetic modification and breeding of small rodents

Surgery, biopsy, marking

Model	Access	Examples	Exposure to pain (degree and duration)	Length of analgesic treatment	Animal species	Proposed treatment
Vasectomy	Abdomen ventral	production of infertile males (for foster mothers with pseudocyesis)	minor to moderate pain for 1 day	1 day	mouse rat	NSAIDs, metamizole
Epidydectomy	scrotum	production of infertile males (for foster mothers with pseudocyesis)	minor to moderate pain for 1 day	1 day	mouse rat	NSAIDs, metamizole
Embryo transfer	abdomen dorso-lateral	hygienic sanitation; embryo transfer after cryopreservation, pronuclear injection, blastocyst injection, in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI)	minor to moderate pain for 1 day	1 day	mouse rat	NSAIDs, metamizole
Implantation of ovaries	abdomen dorso-lateral	preservation of mouse lines by transplantation of ovaries	minor to moderate pain for 1 day	1 day	mouse rat	NSAIDs, metamizole
Biopsy for extraction of DNA	tail tip ≤ 2 mm, first-time auricle hair follicle rectum oral cavity	cell extraction for genotyping by means of PCR: amputation of tail tip, ear notching, ear punching, hair plucking, rectal smear, oral cavity smear and lavage of the oral cavity	minor pain, no analgesia necessary		mouse rat	
	tail tip > 2 mm or repeated amputation of the tail tip	sampling for Southern Blot, new tail tip biopsy for new PCR	minor pain for ≤12 Stunden	12 hours	mouse rat	NSAIDs, metamizole (Depending on biopsy size and activity of the analgesic, a one-time application is often sufficient.)

Marking	ear punching, ear notching, application of ear tags, tail tattooing	identification	minor pain, no analgesia necessary	none	mouse rat	
	transponder application in mice		Depending on the transponder and animal size (adult, outbreeding vs young animal, inbreeding), pain can be of a minor to moderate degree and can last up to 1 day.	0 - 24 hours	mouse	only relevant for mice, NSAIDs, metamizole (one-time)

9 Pain management pharmacy

For postoperative analgesia in an experimental unit, it will usually be sufficient to have one substance of each substance group in stock (1. opioids, 2. antipyretics, 3. NSAIDs, 4. local analgesics, 5. analgesic anaesthetics). A prescription anaesthetic (opioid) is indispensable. The following substances can be used for almost any species in the majority of projects.

Supply of p.op. analgesics:

Examples:

1. Buprenorphine
2. Metamizole
3. Carprofen (in place of NSAIDs of a newer generation, also meloxicam, flunixin meglumine, tepoxalin)
4. Bupivacaine
5. Ketamine, methadone (after effect in postoperative phase)

Other pharmaceutical drugs can be necessary depending on the study design.

Studies show that in 95% of all cases adequate analgesic treatment of animals can be achieved by administration of buprenorphine, metamizole or carprofen only or by combination of them.

Main indicators and contraindications for Buprenorphine, Carprofen, and Metamizole			
	Buprenorphine	**Carprofen**	**Metamizole**
Particularly suited for ...	moderate to severe pain of all kinds	inflammatory pain of all kinds, also for injuries and surgery, well suited for preventive treatment	non-inflammatory pain, particularly cramps and spasms of hollow organs, and after abdominal surgery
Not suited for ...	examining GI tract motility and bile excretion	examinations involving inflammations	animals for whom frequent applications are too stressful, particularly i.m.; cats as they tend to salivate a lot

Dosage instruction:

Compile a dosage table for all animal species and administered compounds.

Examples for pain management with Buprenorphine, Carprofen and Metamizole			
	Buprenorphine (mg/kgBW)	**Carpofen (mg/kgBW)**	**Metamizole (mg/kgBW)**
Sheep	0,001 - 0.01 i.v./i.m./s.c., 6 - 12h	4,0 i.v./i.m./s.c./p.o., 24h (Welsh et al. 1992)	25 - 50 i.v./i.m. 6h
Pig	0,005 - 0,05 - 0.1 i.v./i.m./s.c. 8-12h	4,0 i.v./i.m./s.c./p.o., (12 -) 24h	25 - 50 i.v./i.m.(p.o., 6h
Dog	0,01 - 0,02 i.v./i.m./s.c. 8-12h	4 i.v./i.m./s.c./p.o. 12-24h	20 - 50 i.v./i.m. 4h
Cat	0,005 - 0,01 i.v./i.m./s.c. 8-12h	2 - 4 i.v./i.m./s.c./p.o. 12 - 24h	20 - 50 i.v./i.m. 4-6h
Rabbit	0,01 - 0,05 i.m./s.c./i.v. 6-12h	4 - 5 i.v./i.m./s.c. 12-24h	20 - 50 i.v./i.m. 4h 3 - 5 drops p.o. 4h

Examples for pain management with Buprenorphine, Carprofen and Metamizole			
	Buprenorphine (mg/kgBW)	**Carpofen (mg/kgBW)**	**Metamizole (mg/kgBW)**
Guinea pig	0,05 - 0,5 s.c. 6-12h	4 i.m./s.c. 12h	80 p.o., s.c.
Rat	0,03 - 0,05 s.c. 6-12h	4 - 5 i.v./s.c. 24h	100 p.o., s.c.
Gerbil		4 s.c. 24h	100 p.o., s.c.
Hamster		4 s.c. 24h	100 p.o., s.c.
Mouse	0,05 - 0,1 s.c. 6-12h	5 s.c. 12h	200 p.o., s.c.

Pain management with ketamine

Ketamine in non-anaesthetic doses has recently been successfully used for perioperative pain treatment. In low doses, characteristic side effects of ketamine do not appear. A combination of ketamine with opioids is sensible as ketamine also prevents opiate-induced hyperalgesia. Moreover, the two substances have a potentiating effect.

It is most sensible to include ketamine in the standard anaesthetic protocol for dogs and cats, for example, by giving a preoperative bolus of 0,5 mg/kg. During surgery, a continuous drip infusion of 10 - 30 µg/kg min-1 is recommended, so is a further post-operative continuous drip of 2 µg/kg min-1 for 18 h.

Also, for burnt dogs, p.o. administration of 10 mg/kg 4x a day can be sensible (Joubert 1998).

Legal requirements:

Legal requirements for pain management must be met. In Germany they involve the Medicinal Products Act, Veterinary Dispensary Law and Drug Regulations, and Narcotics Act.

10 Reference list

Albanese J, Viviand X, Potie F, Rey M, Alliez B, Martin C (1999) Sufentanil, fentanyl, and alfentanil in head trauma patients: a study on cerebral hemodynamics. Crit Care Med 27(2): 407-11

Arras M, Rettich A, Cinelli P, Kasermann HP, Burki K (2007): Assessment of postlaparotomy pain in laboratory mice by telemetric recording of heart rate and heart rate variability. BMC Vet Res. 3:16

Arras M, Rettich A, Seifert B, Käsermann HP, Rülicke T (2007): Should laboratory mice be anaesthetized for tail biopsy? Lab Anim. 41(1):30-45

Beliaev DG, Rudakov VF, Dunaevskii IV, Frdi IA (1985) Effect of analgesics on growth and metastasis of sarcoma 37. Vopr Onkol 31(3): 84-8

Bencsics A, Elenkoc IJ, Vizi ES (1997) Effect of morphine on lipopolysaccharide-induced tumor necrosis factor-alpha production in vivo: involvement of the sympathetic nervous system. J Neuroimmunol 73, 1-6

Blaha MD, Leon LR. (2008): Effects of indomethacin and buprenorphine analgesia on the postoperative recovery of mice. J Am Assoc Lab Anim Sci. 47(4):8-19

Bogduk N (1983) The innervation of the lumbar spine. Spine 8, 286-293

Bonica JJ (1985) Treatment of Cancer Pain: Current Status and Future Needs. In: Advances in Pain Research and Therapy, Vol. 9. Proceedings of the Fourth World Congress on Pain, 589. Fields HL, Dubner R, Cervero F (eds.). Raven Press, New York

Bonica JJ (1990) Cancer Pain. In: The Management of Pain, 400. Bonica JJ (ed.) Lea & Febiger, Philadelphia

Booth NJ (1988) Neuroleptanalgesics, narcotic analgesics, and analgesic antagonists. In: Booth NH, McDonald LE (eds.): Vetrinary pharmacology and therapeutics. Iowa State University Press, Ames

Briggs SL, Sawyer DC, Rech RH, Galligan JJ (1995) Oxymorphone-induced analgesia and colonic motility measured in colorectal distension. Pharmacol Biochem Behav 52(3): 561-3

Brough RJ, Lancashire MJR, Prince JR, Rose MR, Prescott MC, Payne SR, Testa HJ (1998) The effect of diclofenac (Voltarol) and pethidine on uretheric peristalsis and the isotope renogram. Eur J Nucl Med 25: 1520-3

Brower MC, Johnson ME (2003) Adverse effects of local anesthetic infiltration on wound healing. Regional anesthesia and pain medicine 28(3): 233-240

Buerkle H, Pogatzki E, Pauser M, Bantel C, Brodner G, Mollhoff T, Van Aken H (1999) Experimental arthritis in the rat does not alter the analgesic potency of intrathecal or intraarticular morphine. Anesth Analg 89(2): 403-8

Byshovets SN, Treshchinskii AI, Blazhenko IL (1997) The effect of Moradol (butorphanol tartrate) on immunity. Lik Sprava 1: 92-8

Cain CK, Francis JM, Plone MA, Emerich DF, Lindner MD (1997) Pain-related disability and effects of chronic morphine in the adjuvant-induced arthritis model of chronic pain. Physiol Behav 62(1): 199-205

Chadzinska M, Kolaczkowska E, Seljelid R, Plytycz B (1999) Morphine modulation of peritoneal inflammation in Atlantic salmon and CB6 mice. J Leukoc Biol 65(5): 590-6

Chu KS, Chen HP, Kang FC, Tsai YC (2000) Prolonged morphine treatment relieves thermal hyperalgesia in rats with sciatic nerve constriction injury. Kaohsiung J Med Sci 16(1): 20-5

Cinelli P, Rettich A, Seifert B, Bürki K, Arras M (2007): Comparative analysis and physiological impact of different tissue biopsy methodologies used for the genotyping of laboratory mice. Lab Anim. 41(2):174-84

Clark JA, Myers PH, Goelz MF, Thigpen JE, Forsythe DB (1997) Pica behavior associated with buprenorphine administration in the rat. Lab Anim Sci 47, 300-3

Colburn RW, Coombs DW, Degnana CC, Rogers LL (1989) Mechanical visceral pain model: chronic intermittent intestinal distension in the rat. Physiol Behav 45(1): 191-7

Committee of pain and distress in laboratory animals (1992): Recognition and alleviation of pain and distress in laboratory animals. National Academic Press, Washington DC

Committee on Recognition and Alleviation of Distress in Laboratory Animals (2008): Recognition and alleviation of distress in laboratory animals. National Academic Press, Washington DC

Committee on Recognition and Alleviation of Pain in Laboratory Animals (in Bearbeitung): Recognition and alleviation of pain and distress in laboratory animals. National Academic Press, Washington DC

Cooper DM, Hoffman W, Tomlinson K, Lee HY (2008): Refinement of the dosage and dosing schedule of ketoprofen for postoperative analgesia in Sprague-Dawley rats. Lab Anim (NY). 37(6):271-5

Cowan A, Doxey JC, Harry EJ (1977) The animal pharmacology of buprenorphine, an oripavine analgesic agent. Br J Pharmacol 60(4): 547-54

Danzebrink RM, Green SA, Gebhart GF (1995) Spinal mu and delta, but not kappa, opioid-receptor agonists attenuate responses to noxious colorectal distension in the rat. Pain 63(1): 39-47

DeClue AE, Cohn LA, Lechner ES, Bryan ME, Dodam JR (2008) Effects of subanesthetic doses of ketamine on hemodynamic and immunologic variables in dogs with experimentally induced endotoxemia: Am J Vet Res 69 (2): 228-32

Deng J, St Clair M, Everett C, Reitman M, Star RA (2000) Buprenorphine given after surgery does not alter renal ischemia/reperfusion injury. Comp Med 50(6): 628-32

Donner GS, Ellison WG, Peyton LC, Crowley N, Szempruch N, Williams JW (1986) Effect of flunixine-meglumine on surgical wound strength and healing in the rat. Am J Vet Res 47: 2247-51

Erhardt W (1992): Postoperative Versorgung. In: Kronberger L (Hrsg.): Experimentelle Chirurgie. Enke Verlag, Stuttgart, 85-92

Erhardt W, Henke J, Haberstroh J (2004): Anästhesie und Analgesie beim Klein- und Heimtier sowie bei Vögeln, Reptilien, Amphibien und Fischen, Schattauer

Fecho K, Maslonek KA, Coussons ME, Dykstra LA, Lysle DT (1994) Macrophage-derived nitric-oxide is involved in the depressed concanavalin A responsiveness of splenic lymphocytes from rats administered morphine in vivo. J Immunol 152, 5845-52

FELASA (1990): The assessment and control of the severity of scientific procedures on laboratory animals. Report of the laboratory animal science association working party. Lab Anim 24, 97-130

FELASA (1994): Pain and distress in laboratory rodents and lagomorphs. Report of the federation of European Laboratory Animal Science Association (FELASA). Working Group on Pain and Distress. Lab Anim 28: 97 -112

Flecknell PA, JH Liles (1991): The effect of surgical procedures, halothane anaesthesia and nalbuphine on the locomotor activity and food and water consumption in rats. Lab Anim 25: 50-60

Flecknell PA (1996): Post–operative care. In: Flecknell PA (ed.): Laboratory animal anaesthesia. Academic Press, London, 127-158.

Flecknell PA, Waterman-Pearson A (2000) Pain management in animals. WB Saunders, London

Flecknell P. (2004): Analgesia from a veterinary perspective. Br J Anaesth. 101(1):121-4

Fürst A (1999) Untersuchungen zum Einfluss der Analgetika Carprofen, Metamizol, Flunixin-Meglumin und Buprenorphin auf die Wundheilung. Vet Med Diss, München

Gärtner K (2002) Zur Beurteilung des basalen und guten Wohlbefindens von Versuchstieren und von "enrichments". Ethologische, neurobiologische, physiologische Zugänge. Tagungsband der 35. Tagung der GV-SOLAS, Ulm

Gandini R, Cunietti E, Pappalepore V, Ferrari M, Deleo B, Locatelli E, Fasoli A, Liverta C (1983) Effects of intravenous high doses of ketoprofen on blood clotting, bleeding time and platelet aggregation in man. J Int Med Res 11(4): 243-6

Gaveriaux-Ruff C, Matthes HW, Peluso J, Kieffer BL (1998) Abolition of morphine-immunosuppression in mice lacking the mu-opioid receptor gene. Proc Natl Acad Sci USA 95(11): 6326-30

Gebhardt DF (1994) Pain and Distress in research animals. In: Smith AC, Swindle MM (eds): Research animal anesthesia, analgesia und surgery. Scientists Centre of Animal Welfare, Maryland, 37-40

Geiger A (2002) Über den Einfluss von Buprenorphin, Carprofen, Flunixin-Meglumin, Meloxicam und Metamizol auf die Knochenheilung bei der Ratte - Unter Einbeziehung der BMP-Aktivität, Knochendichtemessung, Fluoreszenzmarkierung und Histologie. Vet Med Diss, München

Gelgor L, Butkow N, Mitchel D (1992a) Effects of systemic nonsteroidal antiinflammatory drugs on nociception during tail ischemia and on reperfusion hyperalgesia in rats. Br J Pharmacol 105(2): 412-6

Gelgor L, Cartmell S, Mitchell D (1992b) Intracerebroventricular microinjections of nonsteroidal antiinflammatory drugs abolish reperfusion hyperalgesia in the rat`s tail. Pain 50(3): 323-9

Gillingham MB, Clark MD, Dahly EM, Krugner-Higby LA, Ney DM (2001) A comparison of two opioid analgesics for relief of visceral pain induced by intestinal resection in rats. Contemp Top Lab Anim Sci 40(1): 21-6

Goldkuhl R, Carlsson HE, Hau J, Abelson KS (2008): Effect of Subcutaneous Injection and Oral Voluntary Ingestion of Buprenorphine on Post-Operative Serum Corticosterone Levels in Male Rats. Eur Surg Res. 41(3):272-278

Grosse M, Kohn B, Nürnberger M, Ungemach FR, Brunnberg L (1999) Klinische Wirksamkeit und Verträglichkeit von Meloxicam nach der Operation des Kreuzbandes beim Hund. I und II. Kleintierprax 44, 93-105, 155-164

GV-SOLAS (1995): Schmerz und Distress bei Labornagern und Kaninchen. Bericht der Arbeitsgruppe Schmerz und Distress der FELASA. Gelbes Heft der GV-SOLAS

Haberkern S (2002) Zum Einfluss der Analgetika Carprofen, Metamizol, Meloxicam, Flunixin-Meglumin und Buprenorphin auf die Knochen- und Wundheilung unter besonderer Berücksichtigung klinischer, hämatologischer und biomechanischer Aspekte - Eine Studie bei der Ratte. Vet Med Diss, München

Hackbarth H und Lückert A (2000): Tierschutzrecht - Praxisorientierter Leitfaden. Jehle, München

Haskins SC (1992),: Postoperative analgesia. In: Haskins SC, Klide AM (eds.): Opinions in small animals anesthesia. W.B. Saunders Company, Philadelphia, 353-356.

Hall TJ, Jagher B, Schäublin M, Wiesenberg I (1996) The analgesic drug buprenorphine inhibits osteoclastic bone resorption in vitro, but is proinflammatory in rat adjuvant arthritis. Inflamm Res 45(6): 299-302

Hardie EM, Kolata RJ, Rawlings CA (1983) Canine septic peritonitis: treatment with flunixin meglumine. Circ Shock 11(2): 159-73

Hardie EM, Rawlings CA, Shotts EB, Waltman DW, Rakich PM (1987) Escherichia coliinduced lung and liver dysfunction in dogs: effects of flunixine meglumine treatment. Am J Vet Res 48(1): 56-62

Henke J, Brill T, Schäfer B, Korbel R, Erhardt W. (1999): Modernes Schmerzmanagement beim Versuchstier. Der Tierschutzbeauftragte 8(1): 14-20

Henke J, Erhardt W (2001) Schmerzmanagement beim Klein- und Heimtier. ENKE, Stuttgart

Herr G, Reis HJ, Küsswetter W, Rechenbach R (1990) The influence of nonsteroid antiinflammatory drugs on experimentally induced heterotopic ossification. Fundamentals of bone growth: methodology and applications, Proc 3rd Intern Conf Univ Calif, Los Angeles, chap 43

Hirschowitz BI (1994) Nonsteroidal antiinflammatory drugs and the gastrointestinal tract. Gastroenterol 2(3): 207-23

Hocking PM, Gentle MJ, Bernard R, Dunn LN (1997) Evaluation of a protocol for determining the effectiveness of pretreatment with local analgesics for reducing experimentally induced articular pain in domestic fowl. Res Vet Sci 63(3): 263-7

House RV, Thomas PT, Bhargave HN (1995) In vitro evaluation of fentanyl and meperidine for immunomodulatory activity. Immunol Lett 46(1-2): 117-24

IASP (1994) Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy, edited by H. Merkey and N. Bogduk, IASP Press, Seattle

Jackson HC, Griffin IJ, Nutt DJ (1993) Buprenorphine-cocaine interactions in mice: effect on locomotor activity and hole-dipping behaviour. J Pharm Pharmacol 45(7): 636-40

Jacobson C (2000) Adverse effects on growth rates in rats caused by buprenorphine administration. Lab Anim 34(2): 202-6

Jage J (1997) Schmerz nach Operationen. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart

Jenkins WL (1987): Pharmacological aspects of analgesic drugs in animals: An overview. JAVMA 91: 1231-1240

Jensen TS, GEbhart GF (2008) New pain terminology: a work in progress. Pain 140(3): 399-400

Jessen L, Christensen S, Bjerrum OJ (2007) The antinociceptive efficacy of buprenorphine administered through the drinking water of rats. Lab Anim. 41(2):185-96

Jones MK, Wanh H, Peskar BM, Levin E, Itani RM, Sarfeh IJ, Tarnawski AS (1999) Inhibition of angiogenesis by nonsteroidal antiinflammatory drugs: Insight into mechanisms and implications for cancer growth and ulcer healing. Nature Medicine 5(12): 1418-23

Joubert K (1998) Ketamine hydrochloride-an adjunct for analgesia in dogs with burn wounds. J S Afr Vet Assoc 69(3):95-7

Jurna I (1998) Analgetika-Schmerzbekämpfung. In: Forth W, Henschler D, Rummel W, Starke K (eds.) Allgemeine und spezielle Pharmakologie und Toxikologie. BI Wissenschaftsverlag

Kerr FWL (1961) Structural relation of trigeminal soinal tract to upper cervical roots and the solitary nucleus in the cat. Exp. Neurol. 4,134-148

Kigoshi S (1981) Effect of pentazocine on Ehrlich ascites tumor cells. Jpn J Pharmacol 31(5): 781-5

Kirkaldy-Wills WH (1988) Managing Low Back Pain. Churchill Livingstone, New York

Kitchell RL, RD Johnson (1985): Assessment of pain in animals. in: Moberg GP(Hrsg.): Animal Stress. MD: Am. Physiol. Soc., Bethesda

Klee S und Ungemach FR (1997) Die arzneimittelrechtliche Situation der Kleintierpraktiker. Tierärztl Prax 25, 463-7

Knight EV, Kimball JP, Keenan CM, Smith IL, Wong FA, Barrett DS, Dempster AM, Lieuallen WG, Panigrahi D, Powers WJ, Szot RJ (1996) Preclinical toxicity evaluation of tepoxalin, a dual inhibitor of cyclooxygenase and 5-lipoxygenase, in Sprague-Dawley rats and beagle dogs. Fundam Appl Toxicol 33(1): 38-48

Kofke WA, German RH, Garman R, Rose ME (1999) Opioid neurotoxicity: fentanyl-induced exacerbation of cerebral ischemia in rats. Brain Res 818(2): 326-34

Krahl K (2001) Untersuchungen zum Einfluss der Analgetika Meloxicam, Tolfenaminsäure, Ketoprofen und Buprenorphin auf die Wundheilung am Modelltier Ratte, unter besonderer Berücksichtigung zytologischer und histologischer Parameter. Vet Med Diss, München

Krischak GD, Augat P, Sorg T, Blakytny R, Kinzl L, Claes L, Beck A (2007): Effects of diclofenac on periosteal callus maturation in osteotomy healing in an animal model. Arch Orthop Trauma Surg. 127(1): 3-9

Kuraishi Y (2001) Effects of morphine on cancer pain and tumor growth and metastasis. Nippon Rinsho 59(9): 1669-74

Laird JM, Herrero JF, Garcia de la Rubia P, Cervero F (1997) Analgesic activity of the novel COX2 preferring NSAID, meloxicam in monoarthritic rats: central and peripheral components. Inflamm Res 46(6): 203-10

Larsen R (1998) Postoperative Schmerztherapie. In: Anästhesie (Larsen R, Hrsg.). Urban & Schwarzenberg, München

Lascells BD (2000) Clinical pharmacology of analgesics agents. In: Hellebrekers LJ (ed.): Animal pain. Van der Wees, Utrecht (NL), 85-116

Liles JH, Flecknell PA (1992) The use of nonsteroidal antiinflammatory drugs for the relief of pain in laboratory rodents and rabbits. Lab Anim 26: 241-255

Liles JH, Flecknell PA, Roughan J, Cruz-Madorran I (1998) Influence of oral buprenorphine, oral naltrexone, or morphine on the effects of laparotomy in the rat. Lab Anim 32: 149-61

Lobetti RG, Joubert KE (2000) Effect of administration of nonsteroidal antiinflammatory drugs before surgery on renal function in clinically normal dogs. Am J Vet Res 61(12): 1501-7

Lockwood LL, Silbert LH, Fleshner M, Laudenslager ML, Watkins LR, Maier SF (1994) Morphine-induced decreases in in vivo antibody responses. Brain Behav Immunol 8, 24-36

Löscher W, Kroker R (1999) Arzneimittelrechtliche Bestimmungen. In: Löscher W, Ungemach FR, Kroker R (Hrsg.): Pharmakotherapie bei Haus- und Nutztieren. Parey Buchverlag

Loeser JD (1990) Pain after Amputations: Phantom Limb and Stump Pain. In: Management of Pain, 2nd ed. Bonica JJ (ed.). Lea&Febiger, Philadelphia

Lysle DT, Coussons ME, Watts VJ, Bennett EH, Dykstra LA (1993) Morphine-induced alterations of immune status: dose dependency, compartment specifity and antagonism by naltrexone. J Pharmacol Exp Therap 265, 1071-8

Makman MH (1994) Morphine receptors in immunocytes and neurons. Adv Neuroimmunol 4, 69-82

Mayer C (1997) Medikamentöse Schmerztherapie In: Diener HC, Mayer C (Hrsg.): Das Schmerztherapiebuch. Urban und Schwarzberg, Baltimore 307-352

McGuire EJ, DiFonzo CJ, Martin RA, de la Iglesia FA (1986) Evaluation of chronic toxicity and carcinogenesis in rodents with the synthetic analgesic, tilidine fumarate. Toxicol 39(2): 149-63

Mendelson JH, Mello NK, Teoh SK, Lloyd-Jones JG, Clifford JM (1989) Naloxone suppresses buprenorphine stimulation of plasma prolactin. J Clin Psychopharmacol 9(2): 105-9

Menke H, Vaupel P (1988) Effect of injectable or inhalational anesthetics and of neuroleptic, neuroleptanalgesic, and sedative agents on tumor blood flow. Radiat Res 114(1): 64-76

Menninger H, Georgi J (1993) Rheumaschmerz In: Lehrbuch der Schmerztherapie. Zenz M, Jurna I (Hrsg.) Wiss. Verl.-Ges., Stuttgart

Merskey H (1983): Classification of chronic pain. Pain suppl. 3.

Mieszczak C, Winther K (1993) Lack of interaction of ketoprofen with warfarin. Eur J Clin Pharmacol 44(2): 205-6

Mooney V (1987) Presidential address, International Society for the Study of Lumbar Spine, Dallas: Where is the pain coming from? Spine 12, 754-759

Morton DB, PHM Griffiths (1985): Guidelines on the recognition of pain, distress and discomfort in experimental animals and an hypothesis for assessment. The Vet Rec 20, 431-436

Nätscher (2002) Histologische Untersuchungen zum Einfluss der Analgetika Carprofen, Metamizol, Flunixin-Meglumin und Buprenorphin auf die Wundheilung bei der Ratte. Vet Med Diss, München

Nakamoto K, Kamisaki Y, Wada K, Kawasaki H, Itoh T (1997) Protective effect of acetaminophen against acute gastric mucosal lesions induced by ischemia-reperfusion in the rat. Pharmacol 54(4): 203-10

Nelson CJ, Dykstra LA, Lysle DT (1997) Comparison of the time course of morphine’s analgesic and immunologic effects. Anesth Analg 85, 620-6

Ni X, Gritman KR, Eisnenstein TK, Adler MW, Arfors KE, Tuma RF (2000) Morphine attenuates leukocyte/endothelial interactions. Microvasc Res 60: 121-30

Niemi T, Tanskanen P, Taxell C, Juvela S, Randell T, Rosenberg P (1999) Effects of nonsteroidal antiinflammatory drugs on hemostasis in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg Anesthesiol 11(3): 188-94

Osborne NN, Schwarz M, Pergande G (1996) Protection of rabbit retina from ischemic injury by flupirtine. Invest Ophthalmol Vis Sci 37(2): 274-80

Pachtner D (1998) Die Anwendung eines langwirksamen Neuroleptikums bei Laborratten - Verhaltenstests und klinische Relevanz. Vet Med Diss, Universität München

Pacifici R, Patrini G, Venier I, Parolaro D, Zuccaro P, Gori E (1994) Effect of morphine and methadone acute treatment on immunological activity in mice: pharmacokinetic and pharmacodynamic correlates. J Pharmacol Exp Ther 269(3): 1112-6

Parton K, Balmer TV, Boyle J. Whittem T, MacHon R (2000) The pharmacokinetics and effects of intravenously administered carprofen and salicylate on gastrointestinal mucosa and selected biochemical measurements in healthy cats, J Vet Pharmacol Ther 23(2): 73-9

Pascoe PJ (1992): The case of the routine use of analgesics. In: Haskins SC, Klide AM (eds.): Opinions in smal animals anesthesia. WB Saunders, Philadelphia, 357-358.

Piersma FE, Daemen MARC, vd Bogaard AEJM, Buurman WA (1999) Interference of pain control employing opioids in in vivo immunological experiments. Lab Anim 33, 328-33

Pitschi A (2001) Untersuchungen zum Einfluss der Analgetika Meloxicam, Tolfenaminsäure, Ketoprofen und Buprenorphin auf die Wundheilung bei der Ratte. Vet Med Diss, München

Qian J, Brown SD, Carlton SM (1996) Systemic ketamine attenuates nociceptive behaviors in a rat model of peripheral neuropathy. Brain Res 715(1-2): 51-62

Raja SN, Meyer RA, Campbell JN (1988) Peripheral mechanisms of somatic pain. Anesthesiology 68, 571-590

Roughan JV, Flecknell PA (2001) Behavioural effects of laparotomy and analgesic effects of ketoprofen and carprofen in rats. Pain 90, 65-74

Roughan JV, Flecknell PA (2002): Buprenorphine: a reappraisal of its antinociceptive effects and therapeutic use in alleviating post-operative pain in animals. Lab Anim. 36(3): 322-43. Review

Roughan JV, Flecknell PA (2003): Pain assessment and control in laboratory animals. Lab Anim. 37(2): 172

Roughan JV, Flecknell PA (2004): Behaviour-based assessment of the duration of laparotomy-induced abdominal pain and the analgesic effects of carprofen and buprenorphine in rats. Behav Pharmacol. 15(7):461-72

Rovnaghi CR, Garg S, Hall RW, Bhutta AT, Anand KJ (2008): Ketamine analgesia for inflammatory pain in neonatal rats: a factorial randomized trial examining long-term effects. Behav Brain Funct. 4: 5

Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, Ammatuna M, Panerai AE (2000) The effects of tramadol and morphine on immune response and pain after surgery in cancer patients. Anesth Analg 90(6): 1411-4

Sacerdote P, Bianchi M, Manfredi B, Panerai AE (1997) Effects of tramadol on immune responses and nociceptive threshold in mice. Pain 72(3): 325-30

Sager M (1993): Zur Problematik der Quantifizierung von Schmerzen beim Tier. BMTW 106, 289-293

Schnitzler M, Kilbride MJ, Sebagore A (1992) Effect of epidural analgesia on colorectal anastomotic healing and colonic motility. Reg Anesth 17(3): 143-7

Schwartz LM, Jennings RB, Reimer KA (1997) Premedication with the opioid analgesic butorphanol raises the threshold for ischemic preconditioning in dogs. Basic Res Cardiol 92(2): 106-14

Sengupta JN, Snider A, Su X, Gebhart GF (1999) Effects of kappa opioids in the inflamed rat colon. Pain 79(2-3): 175-85

Sessle BJ (1989) Neural Mechanism of Oral and Facial Pain. Otolaryngol. Clin. North Am 22, 1059-1072

Sherman RA, Sherman CJ, Gall NG (1980) A survey of current phantom limb pain treatment in the United States. Pain 8, 85

Sherman RA, Sherman CJ, Parker L (1984) Chronic phantom and stump pai among American veterans: Result of a survey. Pain 18, 83

Schiwy P (2000) Deutsche Tierschutzgesetze. R. S. Schulz, Starnberg

Simon RH, Arbo TE, Lundi J (1984) Beta-endorphine injected into the nucleus of the raphe magnus facilitates metastatic tumor growth. Brain Res Bull 12(5): 487-91

Shyu WC, Morgenthien EA, Barbhaiya RH (1996) Pharmacokinetics of butorphanol nasal spray in patients with renal impairment. Br J Clin Pharmacol 41(5): 397-402

Slingsby LS (1999) Studies on perioperative analgesia in the dog, cat and rat. PhD thesis. University of Bristol, Bristol, pp 147-182

Sluka KA, Deacon M, Stibal A, Strissel S, Terpstra A (1999) Spinal blockade of opioid receptors prevents the analgesia produced by TENS in arthritic rats. J Pharmacol Exp Ther 289(2): 840-6

Spanos HG (1993) Aspirine failes to inhibit platelet aggregation in sheep. Thromb Res 72: 175-82

Sprotte G, (1993) Gesichtsschmerz In: Lehrbuch der Schmerztherapie. Zenz M, Jurna I (Hrsg) Wiss. Verl.-Ges., Stuttgart

Strigo IA, Duncan GH, Bushnell MC, Boivin M, Wainer I, Rosas Rodriguez ME, Persson J (2005) The effects of racemic ketamine on painful stimulation of skin and viscera in human subjects. Pain 113: 255-264

Strom H, Thomsen MK (1990) Effects of nonsteroidal antiinflammatory drugs on canine neutrophile chemotaxis. J Vet Pharmacol Ther 13(2): 186-91

Strumpf M (1993) Krebsschmerz In: Lehrbuch der Schmerztherapie. Zenz M, Jurna I (Hrsg) Wiss. Verl.-Ges., Stuttgart

Sueoka E, Sueoka N, Kai Y, Okabe S, Suganuma M, Kanematsu K, Yamamoto T, Fujiki H (1998) Anticancer activity of morphine and its synthetic derivate, KT-90, mediated throug apoptosis and inhibition of NF-kappaB activation. Biochem Biophys Res Commun 252(3): 566-70

Takahashi H, Traystman RJ, Hashimoto K, London ED, Kirsch JR (1997) Postischemic brain injury is affected stereospecifically by pentazocine in rats. Anesth Analg 85(2): 353-7

Takeda N, Hasegawa S, Morita M, Matsunaga M, Matsunaga T (1993) Pica in rats is analogous to emesis: an animal model in emesis research. Pharmacol Biochem Behav 45, 817-21

Tatari H, Schmidt H, Healy A, Phillipp H, Brunnberg L (2001) Wirksamkeit und Sicherheit von Meloxicam (Metacam®) in der perioperativen Schmerzbekämpfung bei Hunden während orthopädisch-chirugischer Eingriffe , Kleintierpraxis 46(6)

Tatsuo MA, Carvalho WM, Silva CV, Miranda AE, Ferreira SH, Francischi JN (1994) Analgesic and antiinflammatory effects of dipyrone in rat adjuvant arthritis model. Inflammation 18(4): 399-405

Tobias MD, Henry C, Augostides YG (1999) Lidocaine and bupivacaine exert differential effects on whole blood coagulation. J Clin Anesth 11(1): 52-5

Tseng CS, Tso HS (1993) Effects of opioid agonists and opioid antagonists in endotoxic shock in rats. Ma Zui Xue Za Zhi 31(1): 1-8

Tubaro E, Borelli G, Croce C, Cavallo G, Santiangeli C (1983) Effect of morphine on resistance to infection. J Infect Dis 148, 656-66

Twycross RG, Fairfield S (1982) Pain in far-advanced cancer. Pain 14, 303

Ungemach FR, Kluge K (1998) Für den Tierarzt wichtige betäubungsrechtliche Bestimmungen. Tierärztl Prax 26(K), 224-9

Ungemach FR, Kluge K (1999) Achte Novellierung des Arzneimittelgesetzes-die wichtigsten Änderungen für den Kleintierpraktiker. Tierärztl Prax 27(K), 1-4

Van Bree H, Justus C, Quirke JF (1994) Preliminary observations on the effects of meloxicam in a new model for acute intraarticular inflammation in dogs. Vet Res Commun 18(3): 217-24

Van Hooff JARAM, Baumans V, Brain PR (1995) : Erkennen von Schmerzen und Leiden. In van Zutphen LFM, Baumans V, Beynen AC (Hrsg.): Grundlagen der Versuchstierkunde. Gustav Fischer, Stuttgart, 229-237.

Van Loveren H, Gianotten N, Hendriksen CF, Schuurman HJ, Van der Laan JW (1994) Assessment of immunotoxicity of buprenorphine. Lab Anim 28(4): 355-63

Volker D, Bate M, Gentle R, Gerg M (2000) Oral buprenorphine is antiinflammatory and modulates the pathogenesis of streprococcal cell wall polymer-induced arthritis in the Lew/SSN rat. Lab Anim 34, 423-9

Welsh E, Baxter AM, Nolan AM (1992). Pharmacokinetics of carprofen administered intravenously to sheep. Res Vet Sci 53, 264-266

Wiersema AM, Dirksen R, Oyen WJ, Van der Vliet JA (1997) A method for long duration anaesthesia for a new hindlimb ischaemia-reperfusion model in mice. Lab Anim 31(2): 151-6

Williams BJ, Watts JR, Wright PJ, Shaw G, Renfree MB (1999) Effect of sodium cloprostenol and flunixin meglumine on luteolysis and the timing of birth in bitches. J Reprod Fertil 116(1): 103-11

Wright-Williams SL, Courade JP, Richardson CA, Roughan JV, Flecknell PA (2007): Effects of vasectomy surgery and meloxicam treatment on faecal corticosterone levels and behaviour in two strains of laboratory mouse. Pain. 130(1-2): 108-18

Wu WR, Zheng JW, Li N, Bai HQ, Zhang KR, Li Y (1999) Immunosuppressive effects of dihydroetorphine, a potent narcotic analgesic, in dihydroetorphine-dependent mice. Eur J Pharmacol 366(1-2): 261-9

Zagon IS, McLaughlin PJ (1981) Heroin prolongs survival time and retards tumor growth in mice with neuroblastoma. Brain Res Bull 7(1): 25-32

Zahn PK, Gysbers D, Brennan TJ (1997) Effect of systemic and intrathecal morphine in a rat model of postoperative pain. Anesthesiol 86(5): 1066-77

Zech D, Schug A, Horsch M (1988) Therapiekompendium Tumorschmerz. Perimed, Erlangen

Zhang Y, Wu YX, Hao YB, Dun Y, Yang SP (2001) Role of endogenous opioid peptides in protection of ischemic preconditioning in rat small intestine. Life Sci 68(9): 1013-9

Zylber-Katz E, Caraco Y, Granit L, Levy M (1995) Dipyrone metabolism in liver disease. Clin Pharmacol Ther 58(2): 198-209

Further reading:

Alexander JI, Hill PG (1987) Postoperative pain control. Blackwell, Oxford

Arras M, Rettich A, Cinelli P, Kasermann HP, Burki K (2007): Assessment of post-laparotomy pain in laboratory mice by telemetric recording of heart rate and heart rate variability. BMC Vet Res. 3:16.

Benson GJ, Thurmon JC (1987) Species difference as a consideration in alleviation of animal pain and distress. Journal of the American Veterinary Medical Association 191, 1227 – 30

Booth NH (1988) Veterinary Pharmacology and Therapeutics. 6th edn, chapt. 15, Ames, Iowa, University press

Committee of pain and distress in laboratory animals (1992): Recognition and alleviation of pain and distress in laboratory animals. National Academic Press, Washington DC

Committee on Recognition and Alleviation of Distress in Laboratory Animals (2008): Recognition and alleviation of distress in laboratory animals. National Academic Press, Washington DC

Committee on Recognition and Alleviation of Pain in Laboratory Animals (2009): Recognition and alleviation of pain in laboratory animals. National Academic Press, Washington DC

Crane SW (1987) Perioperative analgesia: a surgeon's perspective. Journal of the American Veterinary Medical Association 191, 1254 – 7

Diener H, Maier C (1997) Das Schmerztherapie Buch. Urban & Schwarzberg München Wien Baltimore

Erhardt W (1992): Postoperative Versorgung. in: Kronberger L (Hrsg.): Experimentelle Chirurgie. Enke Verlag, Stuttgart, 85-92

Erhardt W, Henke J, Brill T (1998) Schmerzwirkung und postoperative Schmerztherapie. Tagungsband der 36. Wissenschaftlichen Tagung der Gesellschaft für Versuchstierkunde, Hamburg: 7. – 10. 9. 1998, 49 - 62

Erhardt W, Henke J, Lendl C (2002) Narkosenotfälle. Enke Verlag, Stuttgart

FELASA (1990): The assessment and control of the severity of scientific procedures on laboratory animals. Report of the laboratory animal science association working party. Lab Anim 24, 97-130

FELASA (1994) Pain and distress in laboratory rodents and lagomorphs. Report of the Federation of European Laboratory Animal Science Association (FELASA). Working Group on Pain and Distress. Lab Anim 28: 97-112

Finck AD, Nagai SH (1981) Ketamine interacts with opiate receptors in vivo. Anesthesiology 55: A241

Fish RE, Brown MJ, Danneman PJ, Karas AZ (2008) Anesthesia and analgesia in laboratory animals, 2nd edition, American College of Laboratory Animal Medicine Series, Elsevier

Fish RE, Brown MJ, Danneman PJ, Karas AZ (2008) Anesthesia and analgesia in laboratory animals, 2nd edition, American College of Laboratory Animal Medicine Series, Elsevier

Flecknell PA (1984) The relief of pain in laboratory animals. Lab Anim 18: 147-60

Flecknell PA (1994) Refinement of animal use – assessment and alleviation of pain and distress. Laboratory Animals 28, 222 – 31

Flecknell PA (1996) Laboratory animal anaesthesia, 2. Aufl. London: Academic Press

Flecknell PA (1997) Analgesia and postoperative Care. Tagungsband der Fortbildungstagung ‘Anästhesie und Analgesie’ der Schweizerischen Gesellschaft für Versuchstierkunde, Basel: 25. – 26.11.1997

Flecknell PA (2008): Analgesia from a veterinary perspective.Br J Anaesth. 101(1):121-4, Review

Flecknell PA, JH Liles (1991): The effect of surgical procedures, halothane anaesthesia and nalbu-phine on the locomotor activity and food and water consumption in rats. Lab Anim 25: 50-60

Flecknell PA, Waterman-Pearson A (2000): Pain management in animals. Ballière Tindall, London

Forth W, Henschler D, Rummel W, Starke K (1998) Allgemeine und spezielle Pharmakologie und Toxikologie, 7. Aufl. Spektrum Akademischer Verlag Heidelberg,

Freye E (1999) Opioide in der Medizin. Springer Berlin Heidelberg

GV-SOLAS (1995) Schmerz und Distress bei Kaninchen. Bericht der Arbeitsgruppe Schmerz und Distress der FELASA.

GV-SOLAS (1995): Schmerz und Distress bei Labornagern und Kaninchen. Bericht der Arbeitsgruppe Schmerz und Distress der FELASA. Gelbes Heft der GV-SOLAS

Hall LW, Clarke KW, Trim CM (1991) Veterinary anaesthesia. Bailliere Tindall, London

Haskins SC, Klide AM (1992) Opinions in small animals anesthesia. W.B. Saunders Company, Philadelphia

Hellebrekers LJ (2000) Animal pain. Van der Wees, Utrecht

Hellebrekers LJ (2001) Schmerz und Schmerztherapie beim Tier. Hannover: Schlütersche Verlagsanstalt

Hendriksen CFM, Koeter HBWM (1991) Animals in biomedical research. Elsevier, Amsterdam, 213-234

Henke J, Brill T, Erhardt W (1998) Die postoperative Versorgung der Versuchstiere. Der Tierschutzbeauftragte 2: 143-6

Henke J, Brill T, Erhardt W (1998) Schmerzbelastung, -erkennung, -behandlung. Tierlaboratorium 21, 117 – 25

Henke J, Brill T, Schäfer B, Korbel R, Erhardt W (1999) Modernes Schmerzmanagement beim Versuchstier. Der Tierschutzbeauftragte 1: 14-20

Henke J, Erhardt W (2001) Schmerzmanagement bei Klein- und Heimtieren. Enke Verlag, Stuttgart

Kitchell RL, RD Johnson (1985): Assessment of pain in animals. in: Moberg GP(Hrsg.): Animal Stress. MD: Am. Physiol. Soc., Bethesda

Kohn DF, Wixson SK, White WJ, Benson GJ (1997) Anesthesia and analgesia in laboratory animals. Academic Press, San Diego

Meyer W, Neurand K (1988) Schmerzempfinden bei Hund und Katze – Von peripheren Rezeptoren und ihrer tiefgreifenden Bedeutung. Effem Report 26, 21 – 35

Morton DB, PHM Griffiths (1985): Guidelines on the recognition of pin, distress and discomfort in experimental animals and an hypothesis for assessment. The Vet Rec 20, 431-436

Muir WW, Hubbell JAE, Skarda RT(1993) Veterinäranästhesie. F.K.Schattauer Stuttgart

Otto K (2001) Schmerztherapie bei Klein-, Heim- und Versuchstieren. Berlin: Parey Buchverlag

Otto K (1998) Intraoperative Systembelastungen durch chirurgische Eingriffe und Anästhesie sowie deren postoperative Beeinträchtigung wichtiger Körperfunktionen und des Stoffwechsels. Tagungsband der 36. Wissenschaftlichen Tagung der Gesellschaft für Versuchstierkunde, Hamburg: 7. – 10. 9. 1998, 42 – 8

Otto K (1998) Analgesie der Versuchstiere. Der Tierschutzbeauftragte 2, 148 – 52

Paddleford RR (1999) Manual of small animal anesthesia. 2. Auflage, Saunders Philadelphia

Paddleford RR, Erhardt W (1992) Anästhesie bei Kleintieren. F.K.Schattauer Stuttgart

Roughan JV, Flecknell PA (2003): Pain assessment and control in laboratory animals. Lab Anim. 37(2): 172

Roughan JV, Flecknell PA (2004): Behaviour-based assessment of the duration of laparotomy-induced abdominal pain and the analgesic effects of carprofen and buprenorphine in rats. Behav Pharmacol. 15(7):461-72

Sager M (1993) Schmerzprophylaxe und Schmerztherapie bei kleinen und großen Haustieren; Tierärztliche Praxis 21: 87-94

Sager M (1993): Zur Problematik der Quantifizierung von Schmerzen beim Tier. BMTW 106, 289-293

Sager M (1996) Empfehlungen zur Schmerzbehandlung beim Versuchstier. TVT-Empfehlung

Scharman W. (1996) Verhütung und Verringerung von Schmerzen und Leiden. In: Alternativen zu Tierexperimenten (Gruber FP, Spielmann H, Hrsg.) Heidelberg: Spektrum Akademischer Verlag

Schiwy P (2000) Tierschutzgesetz. Erster Abschnitt Grundsatz §1(25.05.1998) Deutsche Tierschutzgesetze S.1 Verlag R. S. Schulz

Schwarz K (1996) Analgesie nach operativen Eingriffen bei Versuchstieren. Der Tierschutzbeauftragte 2: 112

Smith AC, Swindle MM DF (1994) Research animal anesthesia, analgesia and surgery. Scientists Center of Animal Welfare, Maryland

Soma LR (1987) Assessment of animal pain in experimental animals. Laboratory Animal Science Special Issue January 1987, 71 – 4

Spinelli JS (1987) Reducing pain in laboratory animals. Laboratory Animal Science Special Issue January 1987, 65 – 70

Striebel HW (1999) Therapie chronischer Schmerzen. 3. Auflage Schattauer Verlag

Thurmon JC, Tranquilli WJ, Benson GJ (1999) Essentials of small animal anesthesia and analgesia. Lippincott Williams & Wilkins Philadelphia

van Zutphen LFM, Baumans V, Beynen AC (1995) Grundlagen der Versuchstierkunde. Gustav Fischer, Stuttgart

Wall PD (1992) Defining pain in animals. In: Animal Pain (Short ChE, von Poznak A, Hrsg.) Edingburgh: Churchill Livingstone

Wall PP, Melzack R (1994) The textbook of pain. Churchill Livingstone, Edinburgh

Waynforth HB, Flecknell PA (1992) Assessment and alleviation of postoperative pain. In: Experimental and Surgical Technique in the Rat (Waynforth HB, Flecknell PA, Hrsg.) 2. Aufl., London: Academic Press

World Health Organization (1986) Cancer Pain Relief. World Health Organization, Genf

11 Appendix

11.1 List of pharmaceutical drugs

Generics	**Exemplary brand names**
Acepromazine	Vetranquil, Sedalin, Prequilan
Acetaminophen [Paracetamol]	Benuron, Paracetamol Ratiopharm, Dafalgan
Acetylsalicylic acid	Aspirin, ASA
Azaperone	Stresnil
Bupivacaine	Carbostesin, Bucain
Buprenorphine	Temgesic, Buprenovet
Butorphanol	Butomidor, Morphasol (CH)
Butylscopolamine + Metamizole	Buscopan
Carprofen	Rimadyl
Diazepam	Valium
Diclofenac	Diclo, Diclofenac Ratiopharm
Etodolac	Lodine (CH), Etogesic (USA)
Fentanyl	Fentanyl-Janssen, Fentanyl-Hexal
Fentanyl patch	Durogesic
Flunixin meglumine	Finadyne
Isoflurane	IsoFlo
Ketamine	Ketasol, Ketamine, Ketavet, Narketan, Ursotamin
Ketoprofen	Romefen
Lidocaine	Xylocain, Xylanest
Meclofenamic acid	Parkemed (Austria)
Medetomidine	Domitor, Sedator
Meloxicam	Metacam
Mepivacaine	Scandicain, Meaverin
Metamizole	Vetalgin, Novalgin
Midazolam	Dormicum, Midazolam
Niflumic acid	
Oxybuprocaine	Novesine
Paracetamol [Acetaminophen]	Benuron, Paracetamol Ratiopharm
Perphenazine	Decentan
Pethidine	Dolantin
Phenylbutazone	Phenylbutazone
Piritramide	Dipidolor
Piroxicam	Piroxicam Hexal

Procaine	Isocaine, Minocain, Procasel
Proxymetacaine	
Propofol	Rapinovet, Disoprivan, Narcofol
Ropivacaine	Naropin
Sevoflurane	Sevorane, SevoFlo
Tepoxalin	Zubrin
Tetracaine	Acoin, Ophtocain
Thiopental	Trapanal
Tilidine	Tilidin-Gödecke
Tolfenamic Acid	Tolfedine
Tramadol	Tramal
Vedaprofen	Quadrisol
Xylazine	Rompun, Xylapan, Xylazine

Exemplary brand names	**Generics**
Acoin	Tetracaine
Aspirin ASA	Acetylsalicylic acid
Benuron	Paracetamol [Acetaminophen]
Bucain	Bupivacaine
Buprenovet	Buprenorphine
Buscopan	Butylscopolamine + Metamizole
Butomidor	Butorphanol
Carbostesin	Bupivacaine
Dafalgan	Paracetamol [Acetaminophen]
Decentan	Perphenazine
Diclo Diclofenac Ratiopharm	Diclofenac
Dipidolor	Piritramide
Dolantin	Pethidine
Domitor	Medetomidine
Dormicum	Midazolam
Durogesic	Fentanyl patch
Etogesic (USA)	Etodolac
Fentanyl-Hexal Fentanyl-Janssen	Fentanyl
Finadyne	Flunixin meglumine
Isocaine	Procaine
IsoFlo	Isoflurane
Ketamine Ketasol Ketavet	Ketamine
Lodine (CH)	Etodolac
Meaverin	Mepivacaine
Metacam	Meloxicam

Midazolam	Midazolam
Minocain	Procaine
Morphasol (CH)	Butorphanol
Narcofol	Propofol
Narketan	Ketamine
Naropin	Ropivacaine
Novalgin	Metamizole
Novesine	Oxibuprocaine
Ophtocain	Tetracaine
Paracetamol Ratiopharm	Paracetamol [Acetaminophen]
Parkemed (Austria)	Meclofenamic Acid
Phenylbutazone	Phenylbutazone
Piroxicam Hexal	Piroxicam
Prequilan	Acepromazine
Procasel	Procaine
Quadrisol	Vedaprofen
Rapinovet	Propofol
Rimadyl	Carprofen
Romefen	Ketoprofen
Rompun	Xylazine
Scandicain	Mepivacaine
Sedalin	Acepromazin
Sedator	Medetomidine
SevoFlo Sevorane	Sevoflurane
Stresnil	Azaperone
Trapanal	Thiopental
Temgesic	Buprenorphin
Tilidin- Gödecke	Tilidine
Tolfedine	Tolfenamic Acid
Tramal	Tramadol
Ursotamin	Ketamine
Valium	Diazepam
Vetalgin	Metamizole
Vetranquil	Acepromazine
Xylanest	Lidocaine
Xylapan Xylazine	Xylazine
Xylocain	Lidocaine
Zubrin	Tepoxalin

11.2 List of abbreviations

ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BE	Base excess
BW	Body weight
DI	Continuous drip infusion
COX-2	Cyclooxygenase-2
ERK2 kinase activity	Extracellular regulated kinase 2 activity
GI tract	Gastrointestinal tract
GLDH	Glutamate lactate dehydrogenase
IFN γ	Interferon γ
IgG	Immunoglobulin G
IL	Interleukin
LPS	Lipopolysaccharide
MAP	Mitogen-activated protein
MODS	Multiple organ dysfunction syndrome
NK cells	Natural killer cells
NMDA receptor	N-methyl-D-aspartate receptor
NSAID	Non-steroidal anti-inflammatory drug
PG	Prostaglandin
PTT	Partial thromboplastin time
TENS	Transcutaneous electrical nerve stimulation
TNF α	Tumor necrosis factor α
γ GT	γ Glutamyl transpeptidase