

Pain

We all have experienced pain at one time or the other, but what is pain? Aristotle considered pain as an emotion, he called pain '*a passion of the soul*' Pain in humans, and probably in animals, is in part an emotion. So pain is a word used by humans to represent one of their experiences. They know what it is without needing to define it. Four centuries ago Descartes described pain in terms of an alarm bell ringing in a bell tower.

Animal pain should not be confused with human pain. Animals and humans share similar mechanism of pain detection, have probably similar areas of the brain involved in processing pain. Animal pain probably serves the same purposes as human pain and it is as important to the animal as pain is to humans. However, animal and human experiences of pain, in response to the same stimulus, may not be identical.

Prevention and alleviation of pain and stress in laboratory animals is an ethical imperative. Animal species differ in how they manifest distress, whether from pain or from other sources and this complicates its recognition.

Veterinarians and researchers should identify and eliminate sources of pain and distress. This might, indirectly, help to reduce the number of animals needed for experimental purposes; uncontrolled pain or distress can increase the variability in experimental data and so require the use of more animals in a study for it to achieve statistical significance.

I: Pain and Analgesics

In the attempt to unravel the pathophysiological background of pain one needs to differentiate the terms nociception and pain.

1. What is (Animal) Pain?

To understand animal pain it is helpful to use the definition of human pain.

'Human' pain:

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (International Association for the Study of Pain, 1979)

Pain refers to the subjective, unpleasant sensation that accompanies damage or near-damage to tissues. It is an 'experience', which is the product of the parts of the brain responsible for mental processing of the noxious stimulus. ***"Pain occurs in the brain"***

From this definition we see that pain is a perception, not really a sensation, in the same way that vision and hearing are. It involves sensitivity to chemical changes in the tissues and then interpretation that such changes are harmful. This *perception* is real, whether or not harm has occurred or occurring. *Cognition* is involved in the formulation of this perception. There are *emotional* consequences, and *behavioral* responses to the cognitive and emotional aspects of pain.

So the purpose of pain is **to warn against damage** and to act as an alarm system so that action can be taken to avoid or minimize injury. And **to learn** that something is harmful.

Pain can be considered to have two components: (1) **physical hurt** or discomfort caused by injury or disease; and (2) **emotional suffering**.

Attitude in the past to Animals and Pain;

- Rene Descartes (1596-1650): “*Animals do have no capacity for reasoning, therefore no perception of pain*”.
- Jeremy Bentham (1748-1832): “*The question is not, can they reason? Nor, can the talk? But, can they suffer?*”

At the moment most people would agree that animals are capable of feeling pain according to the first definition. But it is less clear whether they also feel emotional pain.

Animal pain:

“Animal pain is an aversive, sensory experience representing awareness by the animal of damage or threats to the integrity of its tissues ;(note that there might not be any damage). It changes the animal’s physiology and behavior to reduce or avoid the damage, to reduce the likelihood of its recurrence and to promote recovery” (Molony, 1997)

Nociception

*“The recognition and detection of specific signals in the nervous system. The signals originate in sensory receptors (**nociceptors**) and provide information related to tissue damage.”*

It refers to the system that carries signals of damage and pain from the tissues; it is the physiological event that accompanies pain.

Analgesia

“Absence of Pain”

2. Physiology of nociception

With this introduction we can now begin to follow the pathways by which information is transmitted centrally and is ultimately perceived as pain. It travels to the spinal cord or brainstem as a train of electrical impulses.

“Nociception is born in the dorsal horn, but we don’t call it pain till it reaches the brain”

Noxious Stimulation

There are two different types of tissue stimulation which are important;

- a. **Non-noxious stimulation** is generally used by the animal to make it aware of its position in the environment e.g. by touch, vibration or a limb position. Such stimuli travel rapidly along thick, myelinated ($A\beta$), nerve fibers and rarely produce pain unless the fibers are sensitized e.g. inflammation.
- b. **Noxious stimulation** is used by the animal to make it aware of stimuli of an intensity that could or actually do damage body tissues.

The noxious stimulation is detected by nociceptors which are ‘free’ nerve endings of small myelinated ($A\delta$), and smaller non-myelinated (C), nerve fibers, that have their cell bodies outside the spinal column in the dorsal root ganglion and are named based upon their sensory ends. They can detect mechanical, thermal, and chemical stimuli.

Skin, muscle, bone and other tissues have thousands of nerve endings within a single millimeter. When stimulated these nerves generate action potentials (electrical signals), which travel at various speeds along afferent nerve fibers to the spinal cord and brain. It can take from a few milliseconds to a few seconds for these signals to generate an experience of ‘pain’ or to produce an appropriate physiological and behavioral response e.g. a ‘cry’ and/or withdrawal of the affected limb. We call this process; *transduction* of pain.

Nociceptors that respond to thermal or mechanical stimulation have small diameter, myelinated fibres ($A\delta$ type) that transport at high speed (5-30 m/sec) and in humans are known to be related to a sharp pain sensation and are involved in the reflex withdrawal response. Other nociceptors, labeled polymodal nociceptors, can be activated by stimuli of a chemical or intense thermal (hot or cold) or mechanical nature. Signals are transported by afferent fibres (C type fibres) which are unmyelinated and of a small diameter, with a conduction velocity of 0.5-2 m/sec. Upon activation, these C-type fibres will intensify the original stimulus activity and be responsible for the dull, longer-lasting pain.

It is obvious that within pain physiology there is no stable, pre-determined stimulus-response relationship. The final and total response to nociceptor stimulation depends on the intensity and duration of stimulation as well as on the pre-existing state of neural system activity.

An important conceptual breakthrough in our understanding of pain has been the recognition that the pain we experience in our everyday lives when exposed to noxious stimuli, *physiologic pain*, is qualitatively quite different from the *clinical pain* experienced after frank tissue or nerve injury has occurred.

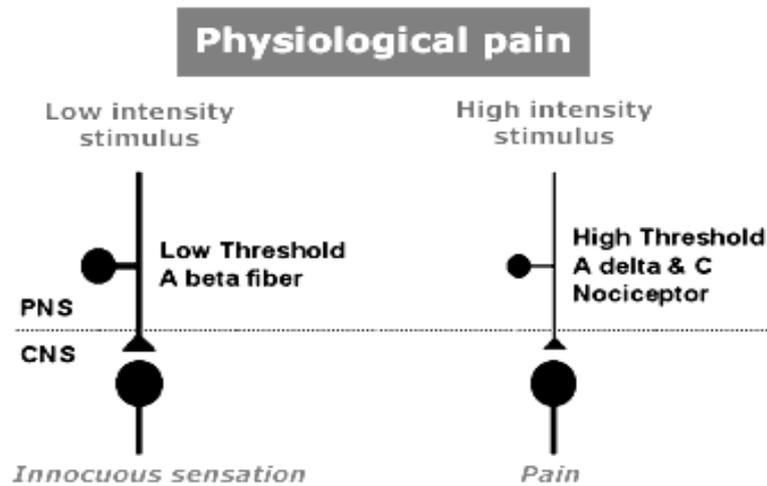


Fig. 1: Physiological Pain

In 'physiological' conditions the low-intensity stimulation results in a non-noxious (tactile) stimulus, while the high-intensity stimulus, following activation of the nociceptor and propagation of the signal by separate afferent pathways, may lead to pain. PNS - peripheral nervous system; CNS - central nervous system

From: Woolf and Chong (1993) Anesth Analg 77; 372-379

Physiologic pain has a high threshold, is well localized and transient, and has a stimulus-response relationship similar to that of other somatosensations. Its fundamental role is to operate as a protective system, warning of contact with potentially damaging stimuli. The stimuli required to elicit this pain are sufficiently different from those that produce innocuous sensations that we can reliably predict whether a given stimulus is likely to produce pain or not. This due to the highly specialized peripheral sensory pathways that subserve these different sensations.

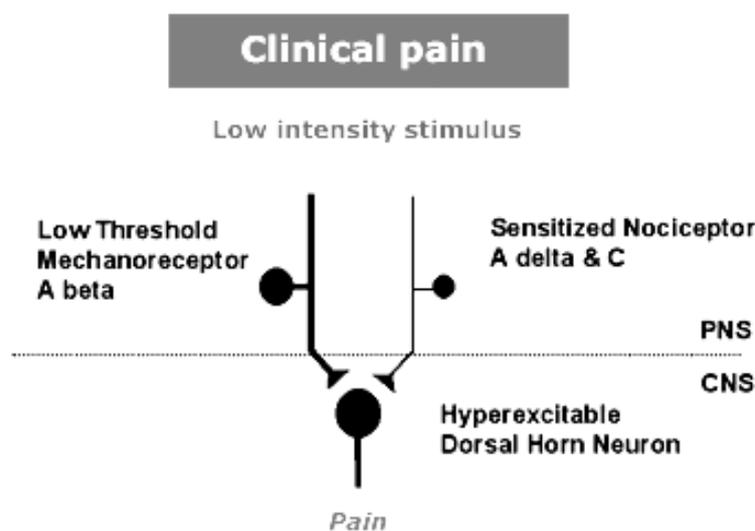


Fig. 2: Clinical Pain

In a pain state, the change in PNS and CNS processing of the sensory information, and subsequent hyperexcitability, results in low-intensity stimuli now being perceived as painful. PNS - peripheral nervous system; CNS - central nervous system.

From: Woolf and Chong (1993) Anesth Analg 77; 372-379

Clinical pain can be divided into inflammatory and neuropathic pain; the former refers to pain associated with peripheral tissue damage, e.g. that produce during surgery, and the latter refers to damage to the nervous system. Both are characterized by changes in sensitivity.

From the periphery, the afferent fibers enter into the dorsal horn of the spinal cord where the processing of the signals takes place. Here, the A δ -fibers connect with motor neurons that are responsible for the reflex withdrawal response.

Locally, at the level of the spinal cord, as well as through descending tracts originating from the medulla, modulation and processing of sensory information will take form depending on circumstances and overall level of activity.

Peripheral sensitization

Next to the primary process initiated with nociceptor activation, the same activation leads to a number of processes that determine the character and intensity of further responses to subsequent stimulation.

Following initial stimulation in the intact, not previously stimulated individual, it is the activation of the high threshold receptors by thermal or mechanical stimuli that lead to pain.

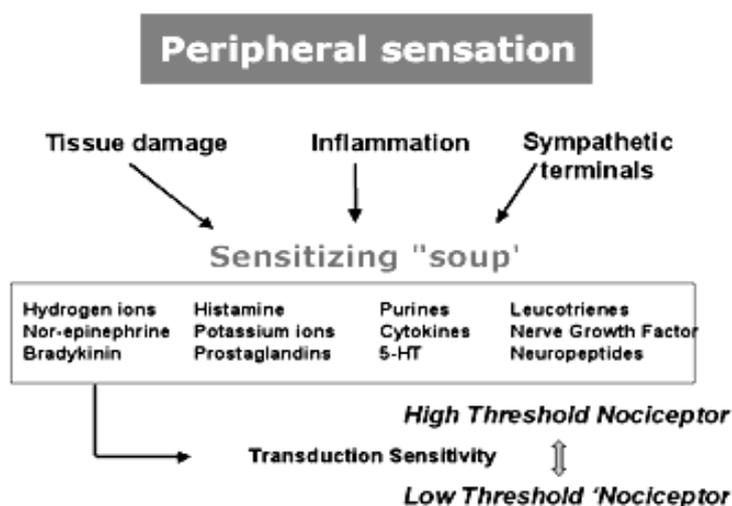


Fig. 3: Peripheral sensitization

Different primary events may create a sensitizing environment around the peripheral nerve ending inducing an increased sensitivity thereof. 5-HT - 5 hydroxytryptamine.

From: Woolf and Chong (1993) Anesth Analg 77; 372-379

When the stimulation is prolonged, the response pattern changes. The inflammatory processes accompanying the tissue trauma account for this change, and subsequent sensitization.

This phenomenon, called peripheral sensitization is, for a large part, dependent on the release of vasoactive amines from damaged tissue and inflammatory cells, and on the release of neuropeptides released from excited nociceptive nerve endings in the injured area.

These latter peptides further stimulate inflammatory cells to set free a whole spectrum of chemical inflammatory mediators, as a result of which the free nerve endings of the nociceptive afferents are 'bathed' in an environment of different kind of inflammatory

mediators. The exposition of the nociceptor to this inflammatory/sensitizing environment results in an increased sensitivity of the (originally) high-threshold nociceptors, to now respond to low-intensity stimuli. The consequence of this being that stimulation that was previously perceived as non-painful/innocuous is now resulting in a painful experience.

The exposition of the nociceptor to a cocktail of those inflammatory mediators and other chemicals liberated by, or in reaction to, tissue damage results in changes in the sensitivity of the transduction mechanism, notably a reduction in the intensity of stimuli necessary to initiate pain so that stimuli that would never normally produce pain begin to do so (*allodynia*). There is also an exaggerated responsiveness to noxious stimuli (*hyperalgesia*) and a spread of hypersensitivity to noninjured tissue (*secondary hyperalgesia*)

Transmission of nociception

The Dorsal Horn Neurons convey pain information from the spinal cord to the brain. In specific regions of the dorsal horn takes the processing of the signals place. Synapses in the dorsal horn act as 'gates' that can open or close to painful impulses. These "gating" effect can be activated by:

- input from the injured area (afferent)
- inhibition of dorsal neurons by the medulla (central 'regulation')

The gate-theory of pain, proposed by Patrick Wall and Ron Melzack, postulates that nociception (pain) is "gated" by non-noxious mechanical stimulation such as rubbing a bumped knee seems to relieve pain by preventing its transmission to the brain. Signals in thick nerve fibers produced, for example by rubbing, can inhibit relay of signals by nociceptive relay neurons (**hypoalgesia**). Pain is also "gated" by signals that descend from the brain to the spinal cord to suppress (and in other cases enhance) incoming nociception (pain) information. Thus **the gate-theory of pain** also helps to explain how the brain can exert control on the relay of nociceptive signals by the spinal cord through pathways from the brainstem to the spinal cord.

There are two ways for nociceptive information to reach the central nervous system;

a. Neospinothalamic tract

'Fast spontaneous pain' travels via type A δ fibers to terminate on the dorsal horn of the spinal cord. Fast pain is felt within a tenth of a second of application of the pain stimulus and is a sharp, acute, prickling pain felt in response to mechanical and thermal stimulation. It can be localized easily if A δ fibers are stimulated together with tactile receptors.

b. Paleospinothalamic tract

'Slow increasing pain' is transmitted via slower type C fibers to laminae II and III of the dorsal horns. Slow pain is stimulated by chemical stimulation, is poorly localized and is described as an aching, throbbing or burning pain.

Nociceptive relay neurons in the spinal cord contribute to local spinal reflex responses such as withdrawal from the stimulus and to complex defensive responses involving the brain and to the experience of pain.

Central sensitization

Primary afferents from peripheral nociceptors enter the spinal cord and terminate in specific regions of the dorsal horn, connecting to fibres ascending to higher centres. Basically afferent fibres terminate on either one of 2 classes of dorsal horn neurons, of which the 'high-threshold nociceptor-specific' neurons respond specifically to noxious stimuli.

Under normal circumstances the so-called 'wide dynamic range' neurons are responsive to non-noxious stimulation, processing this to be perceived as a tactile experience.

When stimulation persists in time, the wide dynamic range neurons become sensitised, leading to hyperresponsiveness. As a consequence, non-noxious stimulation will now result in a painful experience that in duration outlasts the original nociceptive input.

The activated wide dynamic range neurons can be held accountable for the increased sensitivity to mechanical stimulation as well as for the spread of the (hyper)sensitivity of the uninjured tissue surrounding the damaged region.

The increase in spinal excitability will be followed by spatial (receptive field), temporal (duration of stimulus and response) and threshold (sensitivity) increase, together resulting in a hypersensitive and hyperactive state at spinal level.

By an effective prevention of the development of hyperexcitability, a reduction of post-operative pain can be achieved long after the pharmacological duration of action of the analgesic drug.

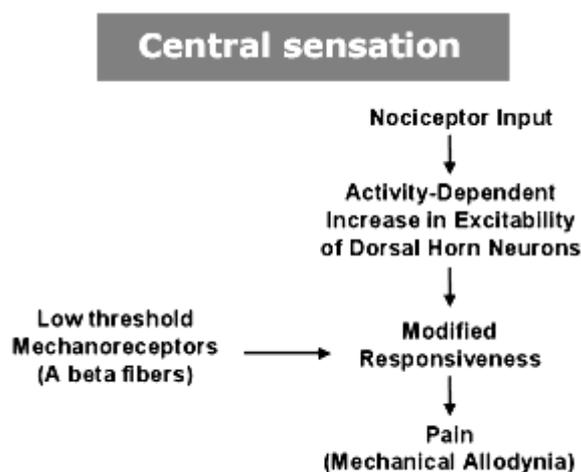


Fig. 4: Central sensitization

Prolonged exposure to noxious stimulation induce an increased level of sensitivity of the central nervous system and subsequently, low-intensity stimuli may become painful rather than innocuous (or non-painful).

From: Woolf and Chong (1993) Anesth Analg 77; 372-379

Just as there is an ascending 'pain' pathway from the body to the brain, there is also a descending pathway, activated by (bio) feedback, psychological factors like stress, drugs and electricity, that allow the brain to modulate the pain sensory. The brain uses this pathway to send chemical substances (transmitters) and nerve impulses to the cells in the spinal cord. Electrical stimulation of the medulla can produce analgesia and has also been shown to inhibit dorsal horn neurons that are activated by nociceptor input. By sending responses back to the periphery, the brain can ordered

the release of opioid peptide-transmitters (endorphins, ed) that can give analgesic effects which are reducing or inhibit pain sensation.

Effects in the Central Nervous System

If the signals are sent to the reticular formation and thalamus, the sensation of pain enters consciousness in a dull poorly localized manner. From the thalamus, the signal can travel to the somatosensory cortex in the cerebrum, when the pain is experienced as localized and having more specific qualities.

Nociception can also cause generalized autonomic responses before or without reaching consciousness to cause pallor, diaphoresis, bradycardia, hypotension, lightheadedness, nausea and fainting

Endogenous analgesia

The body possesses an endogenous analgesia system, which can be supplemented with analgesic drugs to regulate nociception and pain. There is both an analgesia system in the central nervous system and peripheral receptors that decreases the grade in which pain reaches the higher brain areas. The perception of pain can be modified by the body according to gate control theory of pain.

Central; the central analgesia system is mediated by 3 major components : the periaqueductal grey matter, the nucleus raphe magnus and the nociception inhibitory neurons within the dorsal horns of the spinal cord, which act to inhibit nociception-transmitting neurons also located in the spinal dorsal horn.

Peripheral; the peripheral regulation consists of several different types of opioid receptors that are activated in response to the binding of the body's endorphins. These receptors, which exist in a variety of areas in the body, inhibit firing of neurons that would otherwise be stimulated to do so by nociceptors.

Acute Pain vs Chronic Pain

Acute pain plays a protective role: it warns about injury. Acute pain can be produced by transient stimuli, such as venipuncture or brief electric shock. Such pain produces a stress response, but usually does not lead to distress, because the pain is short-lived. In the face of such phasic tissue-damaging stimuli, animals are generally able to adapt their behavior and accept their discomfort. Acute pain also can result from an inflammatory process that originated in damaged tissue, surgery, traumatic injury, or exposure to metabolic, bacterial, or viral disease or toxins. Behavioral responses vary among breeds and species, but the classic signs of inflammation are universal: pain, edema, redness, increased temperature, and loss of function. Those signs are mediated by the release of chemical mediators, such as bradykinin, prostaglandins, leukotrienes, substance P, serotonin, and histamine the inflammatory process produces increased neural activity originating in the response of receptors to tissue-damaging stimuli.

Chronic or persistent pain is different from acute pain and can be harder to recognize, because its onset is slow, its intensity is likely not constant, it is not necessarily associated with an obvious pathologic condition, and it usually does not serve any vital protective function. It is also more likely to lead to distress and maladaptive behaviour.

Animals in chronic pain can be divided into three broad categories: those with a known pathologic condition (e.g., arthritis, cancer, or injury), those in which an organic cause of the pain can be inferred from the results of the clinical examination and history (e.g., pain of musculoskeletal origin, peripheral nerve damage, or disease of the central nervous system), and those with signs that resemble signs in one of the other categories but without obvious cause. Animals in all three categories can exhibit signs of psychological or psychosocial dysfunction.

Some signs are likely to be common to chronic pain of any origin. They include decreased appetite, weight loss, reduced activity, sleep loss, irritability, and decreased mating and reproductive performance (Soma, 1987). Alterations in urinary and bowel activities and lack of grooming are signs often associated with chronic pain, and tearing and lacrimal accumulations around the eyes should be noted. Animals whose pain is chronic or that are moribund might exhibit reduced body temperature, a weak, shallow pulse, and depressed respiration—signs of a poor prognosis.

Chronic pain of the musculoskeletal system is fairly easy to recognize because of lameness or reluctance to move. Some chronic conditions can cause an animal to harm itself; e.g., licking can progress to rubbing, chewing, or scratching, and occasionally self-injury becomes so severe as to mask the cause. Even if a cause is identified and corrected, maladaptive behaviours might persist and require careful diagnosis and treatment

II: Pain management

1. Do Animals Experience Pain? (Peter Singer)

Do animals other than humans feel pain? How do we know? Well, how do we know if anyone, human or nonhuman, feels pain? We know that we ourselves can feel pain. We know this from the direct experience of pain that we have when, for instance, somebody presses a lighted cigarette against the back of our hand. But how do we know that anyone else feels pain? We cannot directly experience anyone else's pain, whether that "anyone" is our best friend or a NHP.

If it is justifiable to assume that other human beings feel pain as we do, is there any reason why a similar inference should not be justifiable in the case of other animals? Nearly all the external signs that lead us to infer pain in other humans can be seen in other species, especially the species most closely related to us--the species of mammals and birds. (*Principle of Analogy*)

In addition, we know that these animals have nervous systems very like ours, which respond physiologically like ours do when the animal is in circumstances in which we would feel pain: an initial rise of blood pressure, dilated pupils, perspiration, an increased pulse rate, and, if the stimulus continues, a fall in blood pressure. Although human beings have a more developed cerebral cortex than other animals, this part of the brain is concerned with thinking functions rather than with basic impulses, emotions, and feelings. These impulses, emotions, and feelings are located in the diencephalon, which is well developed in many other species of animals, especially mammals and birds.

The overwhelming majority of scientists who have addressed themselves to this question agree. Lord Brain, one of the most eminent neurologists of our time, has said:

I personally can see no reason for conceding mind to my fellow men and denying it to animals. [...] I at least cannot doubt that the interests and activities of animals are correlated with awareness and feeling in the same way as my own, and which may be, for aught I know, just as vivid.

The author of a book on pain writes:

Every particle of factual evidence supports the contention that the higher mammalian vertebrates experience pain sensations at least as acute as our own. To say that they feel less because they are lower animals is an absurdity; it can easily be shown that many of their senses are far more acute than ours--visual acuity in certain birds, hearing in most wild animals, and touch in others; these animals depend more than we do today on the sharpest possible awareness of a hostile environment. Apart from the complexity of the cerebral cortex (which does not directly perceive pain) their nervous systems are almost identical to ours and their reactions to pain remarkably similar, though lacking (so far as we know) the philosophical and moral overtones. The emotional element is all too evident, mainly in the form of fear and anger.

That may well be thought enough to settle the matter; but one more objection needs to be considered. [...]

[T]here is a hazy line of philosophical thought, deriving perhaps from some doctrines associated with the influential philosopher Ludwig Wittgenstein, which maintains that we cannot meaningfully attribute states of consciousness to beings without language. This position seems to me very implausible. Language may be necessary for abstract thought, at some level anyway; but states like pain are more primitive, and have nothing to do with language. [...]

Human infants and young children are unable to use language. Are we to deny that a year-old child can suffer? If not, language cannot be crucial. [...]

So to conclude: there are no good reasons, scientific or philosophical, for denying that animals feel pain. If we do not doubt that other humans feel pain we should not doubt that other animals do so too.

Animals can feel pain.

2. Why treat Pain?

Legal and Ethical reasons

Pain in laboratory animals is a major animal welfare problem that must be addressed if we are to apply Russell and Burch's principle of Refinement - "to reduce to an absolute minimum the pain and distress experienced by those animals that are used (in research procedures)".

Beneficial for the Animal and Research

The negative consequences of pain are multiple in nature but can be grouped under the heading of 'stress-response'. As a consequence of this stress response, and next to the discomfort and impaired welfare of the animal, a number of physiological functions will be impaired. The animals are likely to get into a negative energy balance and research has shown that there is clear suppression of the immune status. As a result wound healing will be slowed down, and the incidence of post-surgical complication increases. In the most serious of cases even automutilation is seen. It can be stated that adequate pain relief promotes the animal's overall wellbeing as well as has a positive effect on the speed and quality of post-surgical recovery. At the same time, positive aspects such as reduced mobility and weight bearing will be retained since pain treatment at best achieves a state whereby pain is not completely relieved but has become more endurable. It must be emphasized that stress can still affect experimental results even if an animal under stress seems to be adapting and is manifesting no maladaptive behavioral or physiologic signs.

3. Recognition and Assessment of Pain

One of the more important responsibilities in the use of animals for biomedical research is to recognize clinical signs associated with pain. Without knowledge of their normal and abnormal behavior and appearance, assessment of pain in animals is difficult, because animals are unable to communicate in ways in which they can be readily understood by people. Assessment for pain can be affected by many complicating factors including the age of the animal, degree of apprehension, the nature and frequency of human contacts, and control of visual, auditory, olfactory and tactile stimuli. As such, it is imperative that personnel involved in the care and use of animals are knowledgeable of normal behavior patterns of the species with which they are working and are able to recognize changes from such normal patterns.

Effective pain management can only be achieved and maintained when signs of pain can be assessed reliably and accurately. The experience of pain is unique to each individual, and in man this experience can be described verbally to facilitate pain management. However in animals pain assessment is difficult, often resulting in:

- Analgesics being withheld because the animal is not showing overt signs of pain
- An assumption that since a human who has undergone a similar procedure would require analgesics an animal must also require pain relief, and therefore analgesics are administered

The result of the first scenario is animals that are almost certainly in pain will not receive analgesia. In the second case, since no proper assessment of the degree of pain is made, it is a matter of chance whether an appropriate degree of pain relief is given. In addition, although an initial dose of analgesic is usually beneficial, and unlikely to be detrimental to the animal, in the longer term repeated inappropriate analgesic administration may also cause side effects. Therefore it is clearly preferable to try and assess the animal's pain and adjust the analgesic regimen on the basis of the assessment. Numerous different methods of assessing pain have been developed in man and attempts have been made to apply some of these to animals. In verbal humans, scoring systems or pain questionnaires (e.g. McGill pain questionnaire) are used to evaluate pain and manage analgesic administration directly. However in infants and babies, non verbal or written communication is not possible, leading to similar difficulties with pain assessment to those found in animals.

It is known that objective measures, including heart rate, respiratory rate and body temperature are an unreliable guide to the presence of pain. Therefore current methods to assess clinical pain in animals are based primarily on behavioural observations. However many factors can also influence behaviour adding to difficulties in interpreting how much pain an animal is experiencing. Animals undergoing diagnosis and treatment of clinical disease are usually in an altered environment, leading to changes in their normal behaviour that may mask signs of pain. It is important to interpret pain in each species based on the normal behaviour of that species.

No sign, however, can by itself be regarded as diagnostic of pain, because similar signs occur in conditions in which pain is unlikely. Signs are not all present at one time, and those present on one examination can change by the next. Signs of pain should therefore be considered as a complex group and evaluated together.

Humans often describe pain as sharp, dull, pricking, burning, or itching. Animals cannot relate such descriptions, so pain has to be assessed by observing their behavioral or physiologic reactions. Although many similarities between humans and animals can be used for pain detection, marked differences in pain tolerance must be kept in mind. The anthropomorphizing of pain perception should be tempered by the recognition of the many differences between humans and animals. Pain thresholds are remarkably similar among all species and breeds of animals, but the perceived intensity and tolerance of pain vary among individual animals and in the same animal under different circumstances. Many factors—including strain, species, experience, age, health, and stress—affect pain tolerance. Young animals might have a lower tolerance of acute pain than do older ones. A systemically ill animal might be less tolerant of pain than a healthy one, but a moribund or severely ill animal might be nonresponsive albeit in distress. Some marked differences in pain responses between humans and animals are related to the site of pain. Abdominal surgery is thought to be less painful in four-legged animals than in humans, because humans use their abdominal muscles to a much greater extent in maintaining posture and for walking.

Nonhuman primates show remarkably little reaction to surgical procedures or to injury, especially in the presence of humans, and might look well until they are gravely ill or in severe pain. Viewing an animal from a distance or by video could aid in detecting subtle clinical changes. Loud and persistent vocalization is an occasional

but unreliable expression of pain; it is more likely to signify alarm or anger. Therefore, it should be recognized that a nonhuman primate that appears sick is likely to be critically ill and might require rapid attention. A nonhuman primate in pain has a general appearance of misery and dejection. It might huddle in a crouched posture with its arms across its chest and its head forward with a "sad" facial expression or a grimace and glassy eyes. It might moan or scream, avoid its companions, and stop grooming. A monkey in pain can also attract altered attention from its cagemates; this can vary from a lack of social grooming to attack. Acute abdominal pain can be shown by facial contortions, clenching of teeth, restlessness, and shaking accompanied by grunts and moans. Food and water are usually refused.

4. Therapeutic Options

Except under conditions of general anesthesia, full systemic analgesia can not be achieved by administration of analgesic drugs such as opioids or NSAID's.

Especially when the demand for pain control concerns analgesia for elective surgical procedures, the importance of an adequate systemic analgesic premedication can not be overestimated.

To achieve this analgesia one can choose between different classes of drugs such as opioids or alpha-2 adrenergic agonists. Both classes of drugs provide a good basis for obtaining surgical analgesia and, together with other anesthetic drugs, achieving general anesthesia. Alternatively, one may opt for the use of NSAID's in the anesthetic protocol to further enhance the quality of analgesia during and post-intervention. It has to be realized that although NSAID's may certainly provide an extra dimension in analgesia, they can not alone serve to replace either opioids or alpha-2 agents.

Contrary to the above, local anaesthetics can [under specific circumstances] provide adequate or even complete analgesia, when applied in the correct fashion and for the correct indication.

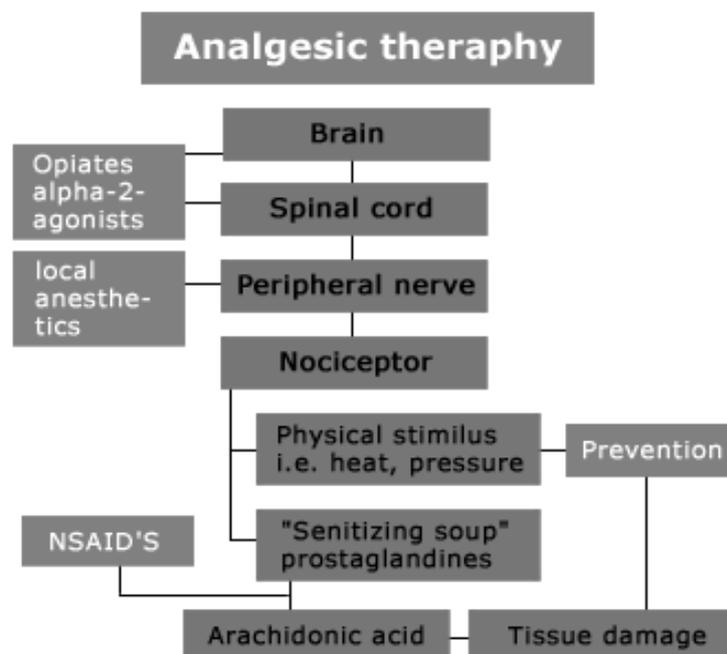


Fig. 5: Schematic presentation of pain pathway and potential therapeutic options for achieving pain relief.

Opioid analgesics

Generally speaking the opioid substances are considered to be the more potent analgesics, although the difference in analgesic potency has been lessened by the introduction of the new and more potent NSAID's. Opioids are widely used for effectively controlling pre- and post-operative pain, but their application does potentially cause a range of side-effects. In addition to the induction of analgesia, side-effects include respiratory depression, increased intracranial pressure, and cardiovascular and behavioral effects.

A class differentiation can be made on account of either the specific opioid receptor (μ , κ , δ and σ) affinity, or the agonist-antagonist character of the opioids, separating the agonist opioids (like methadone, pethidine and fentanyl), from the mixed agonist/antagonist opioids (like buprenorphine, nalbuphine, pentazocine and butorphanol).

The use of agonist agents (like methadone, fentanyl, or the very potent sufentanil) is primarily limited to its application in neurolept-analgesic anesthesia. It is then combined with a (major) tranquilizer like droperidol (methadone/droperidol, fentanyl/droperidol - ThalamonalR) or fluanisone (fentanyl/fluanisone - HypnormR), acepromazine (methadone/acepromazine) or midazolam (sufentanil/midazolam) and can produce an adequate anaesthesia in dogs, rodents, and rabbits. Since the duration of action of fentanyl and sufentanil is only limited (\pm 30 minutes), for prolonged procedures this agent must be repeatedly, or continuously, administered. The longer acting agonist opioids like morphine and methadone are much less potent analgesics than fentanyl and sufentanil, and are more likely to produce respiratory and/or cardiovascular side-effects.

For prolonged pain relief, whether it is following general anaesthesia or not, the mixed agonist/antagonist opioids are commonly used in a wide variety of species. The mixed agonist/antagonist opioid agents (like buprenorphine, nalbuphine, pentazocine and butorphanol) either demonstrate their dual influence on a single type of receptor (i.e. buprenorphine on the μ -receptor) or have an agonistic effect on one, and an antagonistic effect on another type of receptor (i.e. nalbuphine μ -receptor antagonism and κ -receptor agonism). Their dual character of action makes these agents especially useful in pain control following anaesthesia since their effect combines an antagonism of the agonist-induced sedation and (slight) respiratory impairment, while their agonistic action supplies analgesia. Furthermore, some of these mixed agonist/antagonist opioid drugs are relatively long acting.

Buprenorphine couples a slow onset (30-min) with a duration of action of 8 - 10 hrs and a good analgesic effect with little sedative, cardiovascular or respiratory side-effects. This combination of effects makes it excellently suitable for achieving post-anaesthetic analgesia in the different experimental animal species.

Similar results are obtained with pentazocine and butorphanol although some authors have questioned the quality of analgesia with pentazocine. These agents have a weaker potency and a shorter duration of action (approximately 4 hrs) than buprenorphine.

Alpha-adrenergic agents

The agents from the class of α -2 adrenergic drugs, like xylazine and medetomidine, can be categorized as being sedative/analgesic, and consequently clearly induce a

state of sedation together with analgesia.

On account of the sedative/analgesic effect the use of α -2 adrenergic drugs is primarily limited to general anaesthesia in different animal species, where these agents and especially medetomidine, greatly reduce the required dose of any concurrently administered anaesthetic drug. In addition to sedation, drugs from this class produce significant cardiovascular side-effects which include initial hypertension, followed by normo-/hypotension, increased peripheral resistance, a decreased heart rate and cardiac output.

Non-steroidal anti-inflammatory drugs

Another approach to pain relief in the peri-operative period includes the application of Non-Steroidal Anti-Inflammatory Drugs (NSAID's). This class of drugs has traditionally been used in the treatment of chronic, and specifically orthopaedic, pain. The primary reason that limited the use of the earlier representatives of these drugs pre- and per-operatively was related to its mechanism of action [reduction of prostaglandin synthesis]. The combination of these drugs under conditions of reduced perfusion (as is often seen during anaesthesia) could easily induce serious complications, especially regarding renal function.

Recently, drugs from this class such as carprofen have overcome these objections to the pre- and per-operative application. With their potential for pre-operative use formally recognised, it allows for a truly multimodal design of analgesic therapy. Not only does the per-operative presence of a NSAID contribute to the overall analgesic quality, but at the same time it limits the development of sensitisation of pain system. This latter aspect clearly contributes to limiting post-operative pain and facilitates the achievement of adequate pain control post-surgery.

In contrast to the weak analgesic potency ascribed to the earlier NSAID's, the more recently developed NSAID's like ketoprofen, meloxicam, vedaprofen and carprofen have sufficient analgesic potency to effectively combat post-operative pain. These newer agents might thereby be attractive alternatives for, or additives to, opioids in the post-operative phase, whenever the use of opioids is contra-indicated. In addition, the anti-inflammatory effects of the NSAID's provides for specific indications within the 'pain-control' protocol in the post-surgery period, since inflammation usually develops several hours [to days] after the intervention.

Local analgesics

Although a wide variety of applications of local analgesics in relieving pain in animals can be accrued, the characters of many of our animals prevent the large-scale use of local analgesics as a single anaesthetic agent.

A practically viable form of the use of local analgesics is in combination with sedation/light anaesthesia with the local anaesthetic application or the addition of a local analgesic during general anaesthesia to maximize the alleviation of pain. Indications such as dental blocks, axillary plexus block or epidural block prior to the intervention in that specific region can be foreseen in companion animal anaesthesia. Adequate analgesic blockade can be achieved with a single-dose administration of a local analgesic (nerve block, infiltration analgesia), or by way of repeated or continuous administration as with the use of an epidural catheter. An effective local analgesic effect can allow a significant reduction of the anaesthetic depth required or an improved quality of recovery.

Anaesthesia in Non Human Primates

The use of safe and effective anaesthetic techniques can have a major influence on the welfare of animals. Improvement of anaesthetic techniques should be considered an essential aspect of the animal care.

Current views on the use of animals in research give considerable emphasis to the adoption of the 3 R's (*Reduction, Replacement and Refinement*) concepts first described by Russell and Burch in the late 60s. This definition states that 'refinement' involves reducing to a minimum any pain or distress caused to those animals that are used in research. If an animal is anaesthetized, and so is unconscious throughout the procedure, then surely this must be a clear example of refinement? Updating our 'anaesthetic' knowledge and an appropriate use of anaesthesia can make an important contribution to the refinement.

It is also important to keep abreast of new developments in anaesthetic practice, and apply these when they can improve on older methods. Occasionally, unpredictable effects may be encountered, but careful planning, and availability of emergency drugs and equipment can help cope with such problems.

Definitions and terms

- ***Anaesthesia** is defined as a state of controllable, reversible insensibility in which sensory perception and motor responses are both markedly depressed.*

This state can be either *general anaesthesia* -when animals lose consciousness, or *local anaesthesia* –when the loss of sensory and motor function is confined to a specific region.

- ***Analgesia** is the temporary abolition or diminution of pain perception.*
- ***Sedatives** produce drowsiness and appear to reduce fear and apprehension in animals.*
- ***Tranquillisers** produce a calming effect without causing sedation, and at high doses they produce ataxia (unsteady, uncoordinated movement) and depression, but animals are easily roused.*
- ***Muscle relaxants**; this term is usually used to describe neuromuscular blocking agents, which produce paralysis of skeletal muscles.*

Many other drugs used as part of an anaesthetic regime produce varying degrees of muscle relaxation.

I. Pre anaesthetic Management

It is essential that adequate pre-anaesthetic preparations are made before attempting to anaesthetize an animal. Good pre-anaesthetics care will reduce the incidence of many of the complications that can occur during anaesthesia. It is important to consider preparation not only of the animals that are to be anaesthetized, but also the equipment, drugs and personnel that be involved in the procedure.

a. Anaesthetic equipment and personnel

Having determined an anaesthetic protocol, it is important to establish that all the equipment necessary is available, and in good working order. Ensure that sufficient anaesthetic drugs and anaesthetic gasses have been provided not only for the period of anaesthesia but also to cover unexpected additional requirements.

In addition to the anaesthetic agents, drugs needed for coping with emergencies must be readily available.

Monitoring equipment should be switched on, allowed a period to stabilize if necessary, and alarm limits should be reset from the default settings. Heating pads and blankets should be switched on approximately 30 minutes before they are needed.

Personnel involved in the anaesthetic procedure should be familiar with the used equipment and have been briefed on their role in the anaesthetic procedure.

b. The Animal

The single most important factor that can reduce the risks associated with anaesthesia is the use of healthy animals. Anaesthetizing animals that have undetected infections, even if these are causing no signs of disease, usually results in increased mortality and morbidity.

Animals should be obtained 14 days prior to their use, so that they can acclimatize. During this period the metabolic and hormonal changes caused by the stress will return to normal, and the animal caretakers or researchers will have the opportunity to familiarize themselves with the behaviour of the animal and record bodyweight, food and water consumption, etc.

Whatever the health status of the animal, it is useful to carry out some form of clinical examination before induction of anaesthesia.

Non-human primates may vomit on the induction of anaesthesia, or during the recovery, so it is advisable to withhold food for 12 hours. Juveniles or small species such as marmosets, squirrel monkeys and tamarins should only be fasted 6-8 hours to help avoid hypoglycaemia. Water should be withheld 1-3 hours before induction of anaesthesia.

II. Pre-anaesthetic Medication

Historically drugs were given before anaesthesia to reduce the side effects of the anaesthesia e.g. excess secretions during ether anaesthesia. Now the advantage of the pre-anaesthetic medication is:

- Use of sedatives and tranquillisers can reduce aggression and fear or apprehension.
- Use of analgesics can reduce pain and provide “pre-emptive analgesia”
- *Atropine* or *glycopyrrolate* can be given to reduce bronchial and salivary secretions, and to protect the heart from vagal inhibition caused by some surgical procedures (e.g. Manipulation of the viscera, endotracheal intubation).
- Use of sedatives, tranquillisers and analgesics can reduce the amount of other anaesthetic agents required to induce general anaesthesia, so decreasing the undesirable side-effects of these agents and provide a smoother induction of anaesthesia and a smoother recovery.

The use of pre-anaesthetic medication in primates is often essential because of concerns for our personal safety. We should keep in mind that NHP regardless of origin are still wild animals and will resist restraint. The use of pre-anaesthetic sedatives/tranquillisers will help reduce their fear and aggression.

For example, *ketamine*, a dissociative anaesthetic, is frequently used to immobilize a NHP so that it can be handled safely. Administration of the drug may be facilitated by

use of a cage design that allows the animal to be confined for injection. As an alternative to the dissociative anaesthetics, sedatives and tranquillisers can also be used in NHP, but these are not always effective in preventing aggression.

Medetomidine, an alpha 2 agonist, has been used successfully in a wide range of animals to produce a heavy sedation and immobilization. But in NHP it must be used with great care as its sedative effects are less predictable, and some animals may suddenly become alert and may bite their handlers. When combined with *ketamine*, it has effects similar to *ketamine/xylazine* in combination. Animals are immobilized, and a medium plan of anaesthesia is produced. The advantage of this agent is that it can be reversed using a specific antagonist, *atipamezole*. Although the effects of *ketamine* still remain, recovery is generally rapid.

The use of *ketamine* in marmosets has been associated with muscle damage. This is probably related to the low pH of ketamine (3-4), and its injection into relatively small muscle mass of marmosets. For this reason, pre-medication with *alpaxalone/alphadone* is preferable.

Commonly used pre-anaesthetic agents:

1. Anticholinergic Drugs

Anticholinergics block parasympathic stimulation to the cardiopulmonary system and reduce salivary secretion. They are used in combination with sedatives and analgesics as pre-medication to general anaesthesia.

Atropine:

Is the most commonly used anticholinergic agent; however, routine administration is controversial due to the high incidence of associated cardiac dysrhythmias (premature ventricular contractions and sinus tachycardia). It is also recommended for the use in NHP in order to decrease airway secretions, protects the heart from vagal inhibition, which can occur during endotracheal intubation or during surgical procedures. It may also be used to correct any slowing of the heart caused by opioids such as fentanyl.

Avoid the use of atropine if the heart rate is already elevated.

Glycopyrrolate:

Although its mechanism of action is similar to that of atropine, its effects are longer. Glycopyrrolate seems to be less likely than atropine to produce sinus tachycardia. It does not penetrate the CNS because of its difficulty in crossing the blood-brain barrier. It is also less likely than atropine to cross the placental barrier, indicating that it is a selective peripheral anticholinergic agent.

2. Tranquillizers and sedatives

Tranquillizers produce a calming effect without sedation. They have no analgesic properties, and even at high doses that cause ataxia (failure of muscular coordination) and depression, animals are easily aroused. Tranquilizers are useful over a wide range of species, often in combination with other drugs, to lessen the dose of a general anaesthetic and produce a smoother induction and recovery.

Sedatives are used to produce drowsiness and reduce fear and apprehension.

The psychological state of an animal prior to administration of tranquillizers may markedly affect the degree of sedation achieved. Animals that are vicious, intractable

and in a state of excitement may not become manageable except with very high doses!

Phenothiazines: (*promazine, acepromazine*)

These drugs produce sedation, have no analgesic action but they potentiate the action of anaesthetics and narcotic analgesics, and so reduce the dosage required to produce a surgical anaesthesia. The sedation may extend into the post-operative period, so that recovery is smooth.

A moderate hypotension may occur because of the production of peripheral vasodilation. Temperature regulation is depressed and moderate hypothermia may occur. These undesirable effects are well tolerated by normal animals, but the drugs should not be used in animals with any form of fluid deficit (eg dehydration or haemorrhage).

Benzodiazepines: (*diazepam, midazolam*)

Both diazepam and midazolam have marked sedative effects in rodents and rabbits, but their effects in other species are less predictable. They may cause mild excitement and disorientation rather than sedation. They can be administered by a variety of routes and are often used in combination with other agents to produce balanced anaesthesia (potentiate the action of most anaesthetics and opioids). The sedative properties, although pronounced, are not usually sufficient to completely immobilize an animal for minor procedures.

Midazolam has effects similar to diazepam but with a shorter duration of action, it is water-soluble, and so can be mixed with other agents.

Butyrophenones: (*azaperone, droperidol*)

Have similar effects as phenothiazines, but are more potent and cause less hypotension. Droperidol is used in combination with an opioid to produce neuroleptanalgesia.

Alpa-2-adrenergic agonist: (*xylazine, detomidine, medetomidine*)

Xylazine (Rompun[®]) is a sedative and analgesic that acts as a CNS depressant and induces muscle relaxation by inhibiting the transportation of impulses in the CNS. Its major use in animal anaesthesia is in combination with ketamine to produce surgical anaesthesia. This combination has been used in dogs, cats, large animals, NHP and wild animals. It causes respiratory depression and a bradycardia which may progress to a heart block. It also increases the susceptibility of the myocardium to circulating catecholamine's during halothane anaesthesia. Vomiting may occur and gas accumulation due to gastrointestinal atony (lack of normal tone or strength) may be a problem. Xylazine produces profound physiological changes and its safe use requires knowledge of these effects which are often species specific.

Medetomidine (Domitor[®]) can both be used to produce sedation with some analgesia in a wide range of different species. At higher dose rates the effects can be sufficient to immobilize some animals. In NHP its sedative effects are less predictable, and some animals may suddenly become alert and may bite their handlers.

In species that vomit, medetomidine often triggers this reflex. Other side effects including hyperglycaemia, diuresis, and respiratory and cardiovascular

system depression occur. Medetomidine has a lower incidence of those side-effects.

A major advantage of these sedatives is that their action can be reversed by administration of specific antagonists such as atipamezole.

3. Narcotic Analgesic (*morphine, buprenorphin, fentanyl, sufentanil, oxymorphone*)

These compounds can produce moderate sedation and profound analgesia but in some species pre-operative administration will cause hyperactivity and excitement.

These drugs may produce respiratory depression (generally only at high dose rates) and vomiting in primates.

Narcotic analgesics can be used both to provide pre-operative analgesia and to reduce the dose of anaesthetic agents necessary to produce surgical anaesthesia. It is also probable that pre-operative administration of analgesics may reduce the degree of post-operative pain. They are frequently used in combination with sedative agents to provide chemical restraint and analgesia for minor procedures. A number of commercial preparations, which combine a potent opioid with a sedative or tranquilliser, are available, such as 'Hypnorm' (fentanyl and fluanisone)

III. Anaesthesia

General anaesthesia is the induction of a state of unconsciousness with the absence of pain sensation over the entire body, through the administration of anaesthetic drugs. It is used during certain medical and surgical procedures.

Anaesthesia aims to:

- Eliminate pain so that surgical and diagnostic procedures can be carried out humanely (in addition to preventing distress, and movement in response to surgical stimuli, elimination of pain also reduces the risk of shock!).
- Immobilize the animal so that procedures can be carried out safely.
- Produce relaxation of skeletal muscles to reduce or eliminate reflex responses and muscle spasm.

Stages of anaesthesia

Anaesthesia performed with general anaesthetics occurs in four stages which may or may not be observable because they can occur very rapidly:

1. **Induction.** Is the period between the initial administration of the induction medications and loss of consciousness. During this stage analgesia progresses.
2. **Excitement.** Is the period following loss of consciousness and marked by excited and delirious activity. During this stage, respirations and heart rate may be irregular. In addition, there may be uncontrolled movements, vomiting, breath holding, and papillary dilation. Rapidly acting drugs are used to minimize time in this stage and reach stage 3 as fast as possible.
3. **Surgical Anaesthesia.** During this stage, the skeletal muscles relax, and the patient's breathing becomes regular. Eye movements slow, and then stop, and surgery can begin.
4. **Medullary Paralysis.** This stage is also known as "overdose", and occurs when too much medication has been given and the animal has severe brain stem or medullary depression. This results in a cessation of respiration and potential cardiovascular collapse. This stage is lethal without cardiovascular

and respiratory support. This stage should never be reached. Careful control of the amounts of anaesthetics administered prevents this occurrence.

The general anaesthetic regime includes the next phases:

- i. **Induction** of the anaesthesia. To provide a rapidly, calm and safe loss of consciousness in the animal.
- ii. **Maintenance** of the anaesthesia. To keep the animal asleep. In this phase the animal should be unable to perceive painful stimuli and the muscles should be relaxed.
- iii. **Recovery** from the anaesthesia. The rapid return to the normal physiology and behaviour of the animal.

General anaesthesia can be induced using a variety of drugs and techniques for example by **injection** (eg. Propofol), **inhalation** (these can be gases, or volatile liquids which are vaporized before delivery to the animal) or **local** (eg Lidocaine).

Anaesthetic techniques are often selected from just one of these, but it is often beneficial to use two or more techniques in combination, for example isoflurane by inhalation to produce loss of consciousness and some muscle relaxation, and an analgesic such as fentanyl, to block the perception of pain. This approach is called “**balanced anaesthesia**”. The advantage of such an approach is that the undesirable side-effects of the anaesthetic agents can often be minimized. The side-effects of anaesthetics are usually dose dependent. Although it might appear at first to be an unnecessary complication, giving several drugs in combination, at relatively low dose rates, can often result in less side-effect and can also result in more rapid recovery.

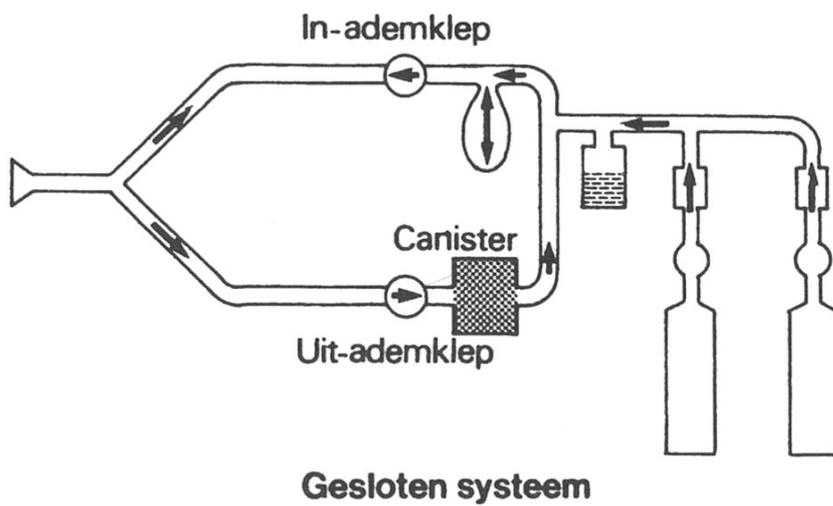
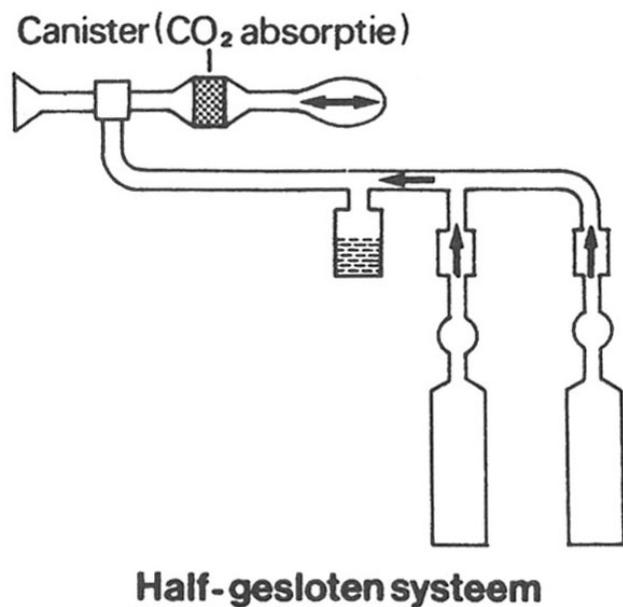
1. Inhalation Anaesthesia

Inhalant anaesthetics have the advantage of requiring minimal detoxification by the body, as they are exhaled through the lungs, and the level of anaesthesia can be easily and rapidly controlled. However, their use requires specialized equipment for administration, and constant monitoring of the patient. Some are explosive or inflammable, or tissue irritants. Chronic exposure to some agents is hazardous to the health of the surgery room personnel.

The speed of induction and recovery depend on the solubility of the anaesthetic in blood. Highly soluble anaesthetics are slow to reach an equilibrium in the blood; therefore, induction and recovery are prolonged. Insoluble anaesthetics reach equilibrium rapidly, making manipulation of anaesthetic depth easier, but also more hazardous due to the potential for rapid overdose!

The use of inhalation anaesthesia requires the following equipment:

- A vaporizer for volatile anaesthetics
- A source of carrier gas usually oxygen and/or air
- A breathing system from which the anaesthetic mixture is inhaled
- A mask or endotracheal tube for connecting the breathing system to the patient



Unnecessary exposure of personnel to gases from volatile anaesthetics must be avoided by use of appropriate scavenger systems. Several reports have suggested a health risk associated with prolonged and repeated exposure to low concentrations of halothane (hepatocellular toxicity), methoxyflurane (renal toxicity) and nitrous oxide (neurologic disease and pernicious anemia). Expired gases should be vented to the exterior or absorbed onto activated charcoal!

Common used inhalation anaesthetics are dividing in two groups.

a. Ether-based volatile agents:

Methoxyflurane is a highly soluble, potent anaesthetic. Because of its low volatility, it may be used safely for induction with anaesthetic chambers, and nose cone maintenance. It produces some respiratory and cardiovascular depression, but less than halothane at comparable depths of anaesthesia. Myocardial sensitization occurs, but not as severe as with halothane. Muscle relaxation and analgesia are good, and it is neither irritating nor explosive in anaesthetic concentrations.

Isoflurane is less potent than halothane or methoxyflurane. It is relatively insoluble which lead to fast inductions and recoveries. It produces a slightly more severe respiratory depression than does halothane, but slightly less depression of the cardiovascular system. There is very little myocardial sensitization to catecholamine's; in fact, isoflurane has the greatest margin of safety with the cardiovascular system of all the inhalant anaesthetics. Isoflurane produces better muscle relaxation than halothane, but has poorer analgesic properties. It undergoes even less biotransformation and is almost completely eliminated in exhaled air. Isoflurane has pungent odour which may cause breath holding during induction. It has no known toxicities, but is expensive!

b. Halogenated hydrocarbons:

Halothane is highly potent and volatile. It should be used only with finely calibrated vaporizers. It produces dose-dependent depression of the cardiovascular system and hypotension. There is direct myocardial depression and sensitization to circulating catecholamines. The analgesia offered by halothane is reasonable, as is muscle relaxation. The vapours are neither explosive ore irritating, but can be hepatotoxic to man!

2. Injection Anaesthesia

Inject able anaesthetic agents can be administered by a variety of routes. Intravenous administration is usually preferable, since this produces the most predictable and rapid onset of action. This enables the drug to be administered to effect to provide the desired depth of anaesthesia. Practical considerations, such as the need of the chemical restraint of NHP, may limit the use of this route.

Administration by intramuscular (i/m), intraperitoneal (i/p) or subcutaneous (s/c) injection is relatively straightforward in most species but the rate of drug absorption, and hence its anaesthetic effects, may vary considerable. It is important to appreciate the very great variation in response to anaesthetics that occurs between animals of different age, and sex!

Common used agents are:

a. **Barbiturates** (pentobarbital, thiopental)

Barbiturates differ from tranquillizers and opioids in that increasing the dose progressively increases the depth of depression until a state of general anaesthesia is reached. They are poor analgesics. Their primary use is in the induction and/or maintenance of general anaesthesia. Barbiturates are potent respiratory depressants and their effects on the cardiovascular system are variable. At intermediate dosages excitement is sometimes induced.

The barbiturates are grouped according to duration of action into long acting (eg. Phenobarbital), short- or intermediate-acting (eg. pentobarbital) and ultra short acting (eg. thiopental, thiamylal). The short- and ultra short acting drugs are commonly used for anaesthesia. Variation in dose response and duration of effect of barbiturates is extreme within and between species; however, in general, short/intermediate barbiturates produce approximately 2-3 hours of anaesthesia and ultra short barbiturates range from 10-20 minutes.

Whenever possible, barbiturates should be administered intravenously, slowly, to effect. Administration by other routes is far less satisfactory, as dosage is more difficult to judge and the anaesthetic effects are less predictable.

Although barbiturates are commonly used, they are often poor choices for general anaesthesia due to poor analgesia, profound cardiovascular effects, high mortality and numerous external factors that can affect dose response and sleeping time. Adequate anaesthesia can be obtained by combining a barbiturate with a tranquillizer, sedative or even an opioid.

b. ***Dissociative anaesthetics*** (ketamine, tiletamine)

Dissociative anaesthetics produce a state of chemical restraint and analgesia characterized by muscle rigidity and dissociation of the mind from the external environment. The eyes remain open, necessitating using protective ointment. Various reflexes, including the blinking reflex and laryngeal reflex, remain intact, and adequate respiration is normally maintained. An increase in heart rate, blood pressure and intracranial pressure frequently occurs. Combination with a tranquillizer is recommended to enhance analgesia and reduce muscle tone.

Ketamine-hydrochloride is the most commonly used member of this group and often used to provide chemical restraint in several species. As mentioned before, it is widely used in Old-world primates, and produces immobility and some analgesia. The depth of anaesthesia is dose related.

Side effects include excessive salivation which may be controlled with atropine, a tendency toward convulsions, and a recovery characterized by excitement, disorientation, and hallucination which may be controlled by tranquillizers and barbiturates. In all cases, a smooth recovery will be facilitated if the patient is left undisturbed in a quiet, darkened environment. Ketamine is usually administered intramuscularly, but it can also be given orally if an IM injection is not possible. It can, however, be injected (4-10 times the IM dose is required) into foods such as bananas, to sedate animals that have escaped from their cages!

Tiletamine is similar to ketamine, but longer lasting and more potent; therefore a smaller dose volume is needed. It is most commonly used in combination with the tranquillizer zolazepam (Telazol[®], Zoletil[®]) which improves muscle relaxation, CNS depression, and emergence from anaesthesia.

c. ***Neuroleptanalgesic combinations***

Fentanyl/fluanisone (Hypnorm[®]), when administered alone, produces sedation and sufficient analgesia for superficial surgery. The degree of muscle relaxation is generally poor, and the high doses needed for more major surgery produce marked respiratory depression. Combining this regime with a benzodiazepine produces surgical anaesthesia with only moderate respiratory depression. The combination has the advantage that it can be partially reversed with a partial agonist such as bupernorphine. This reverses the respiratory depression caused by the fentanyl, but maintains post-operative analgesia. The benzodiazepine antagonist flumazenil can be used to further speed recovery, but repeated doses are needed to avoid resedation!

Fentanyl/droperidol (Innovar Vet[®]) when used alone produces similar effects to Hypnorm[®] but in combination with midazolam its effects are unpredictable and it is best used alone to provide immobility, sedation and analgesia for minor procedures.

Although the use of neuroleptanalgesics has been reported in NHP, they are not widely used because of problems with respiratory depression.

d. ***Propofol***

Should be administered intravenously. Propofol produces short periods of surgical anaesthesia and additional doses can be given to prolong the period of anaesthesia, without unduly prolonging recovery. Propofol can cause transient apnoea if given rapidly as a bolus, but has not been found to be a clinically significant problem! Some hypotension can occur following its administration, but this is not generally a concern in healthy individuals. Mean Arterial blood Pressure (MAP) is often better maintained than with inhalational agents. The dose of propofol required to maintain anaesthesia can be reduced by concurrent administration of opioids. This balanced anaesthetic technique can be used to provide prolonged periods of anaesthesia, with a relatively mild degree of cardiovascular depression. Respiratory depression is often marked however, so it is strongly advised that animals are mechanically ventilated! A number of short acting opioids (μ -agonist) can be used, such as fentanyl and sufentanil. At the end of the period of anaesthesia, respiratory depression caused by the opioid can be reversed by the administration of an agonist/antagonist opioid such as nalbuphine, butorphanol or buprenorphine.

e. ***Steroid anaesthetic agents***

Alphaxalone/Alphadolone (Saffan[®]), when given by deep intramuscular injection, it produces light anaesthesia, and this route is useful in new world primates. After administration of an initial dose i/m, additional drug is given i/v to induce surgical anaesthesia. Anaesthesia can then be maintained by further doses or by continuous infusion of the agent.

Both alphaxalone/alphadolone and propofol are relatively non-cumulative, unlike the barbiturates, so that recovery following prolonged anaesthesia is relatively rapid. The short duration of action of these agents (approximately 10 minutes after a single dose) means that the depth of anaesthesia can be adjusted easily by changing drug infusion rates.

3. Local Anaesthetics

Lidocaine, procaine and bupivacaine may be used as local anaesthetics, they block the transmission of nerve impulses in nerve fibres to a limited area, so complete analgesia can be provided. They can be infiltrated around surgical wounds to provide post-operative analgesia and they can also be used to produce specific nerve blocks. In larger species they can be administered epidurally or intrathecally to produce regional analgesia and anaesthesia. High dose rates can cause cardiovascular disturbance and CNS effects such as convulsions.

IV. Anaesthetic Management – Preventing problems and coping with emergencies

Even during brief periods of anaesthesia, it is important to give attention to supporting the animal's vital body functions:

- Onset of surgical anaesthesia usually results in the loss of all protective airway reflexes, and the animal should be placed in a position with its head and neck extended, to help ensure its airway remains clear and unobstructed.
- Provide oxygen by facemask to prevent the animal becoming hypoxic.
- Anaesthetised animals lose their protective blink reflexes, and the eyes should be protected both from physical damage and from drying. Ophthalmic ointment can be placed in the eyes, (or the eyelids can be taped closed with tape).

Careful monitoring of the patient is important to allow early detection and correction of any problems that may arise. In all species, respiratory and cardiovascular functions are of primary importance, but in small animals in particular, maintenance of body temperature is of critical importance:

- Small animals have a higher surface area to body weight ratio than larger animals, and so lose heat more rapidly. (5-10 degrees C can occur in mice within 15 minutes of induction of anaesthesia)
- Most anaesthetics depress thermoregulation, and this effect, coupled with use of cold fluids, shaving and preparation of the surgical site and use of cold anaesthetic gases can rapidly result in severe hypothermia.

To avoid problems:

- Monitor body temperature using an electronic thermometer.
- Small mammals should be placed on a heating pad, and if necessary covered in a special blanket. (bubble packing or aluminium foil)
- Avoid using excessive amounts of skin disinfectants, minimize the shaved area at the site of surgery, and avoid unnecessary exposure of the abdominal viscera.
- Warm all fluids to body temperature before administration.

Respiratory function

Observing the movements of the chest can be used to monitor the pattern and depth of respiration, although this becomes difficult once surgical drapes have been placed. If a reservoir bag is present on the anaesthetic circuit used, then this can be observed to assess the rate and depth of respiration.

Although both the pattern and the rate of respiration changes during anaesthesia, this varies greatly depending upon the anaesthetic regimen used. Becoming familiar with one or two regularly used regimens allows changes to be interpreted more reliably. In general once anaesthesia is induced, respiratory rate reduces markedly. A reduction to less than 50% of the estimated normal; respiratory rate should give cause for concern. It is more usual to see gradual changes in rate, rather than a sudden reduction, so keeping an anaesthetic record is helpful when assessing the state of the animal during anaesthesia.

- Pulse oxy-meters can be used to monitor both the adequacy of oxygenation, and also the heart rate, but not all instruments function in small animals. The high heart rates may exceed the upper limits of the monitor, and the low

signal strength may not be detected. A reliable signal can usually be obtained from a toe, the tail, tongue and ear.

- Capnographs, which measure the concentration of carbon dioxide in expired air, are extremely useful for monitoring respiration. When an animal is breathing normally, the end-tidal carbon dioxide is between 5 and 6%. Although these instruments can be used to monitor respiratory function in small animals, mainstream capnographs (which are placed in the anaesthetic breathing circuit close to the animal) introduce too much equipment dead space and cannot be used in small animals. Side-stream capnographs (which extract gas out of the anaesthetic circuit to be analysed) can be used, but the volume of gas sampled may be very large in relation to the animal's tidal volume, so the measurements made may not be very accurate.

If respiratory depression occurs, it must be monitored carefully, and if severe depression (<40% of estimated resting rate) or arrest occurs, it must be treated promptly. If severe hypoxia occurs, and is uncorrected, this can lead to cardiac failure.

- Administer oxygen if this is not already being done. It is advisable to provide oxygen immediately following induction of anaesthesia with injectable anaesthetics, since all of the agents used produce some degree of respiratory depression.
- Assist ventilation – if an endotracheal tube is in place, if not, assist ventilation by manually compressing the thorax, and providing oxygen by facemask. Attempts to ventilate the lungs using a facemask are often relatively ineffective.
- Administer a respiratory stimulant such as doxapram (10 mg/kg)

Endotracheal intubation

Assisting ventilation is considerably easier if the animal has been intubated, and this is an easy technique to master in NHP.

In general, intubation is made easier if an appropriately sized laryngoscope blade is obtained, so that the larynx can be visualised clearly. In smaller species in which the oropharyngeal opening is relatively small, it is often easier to use an introducer to straighten the endotracheal tube and guide it into the larynx. An introducer is also helpful when intubating NHP, as although visualisation of the larynx is easy to achieve, the larynx is relatively mobile, making insertion of an endotracheal tube difficult in smaller primates.

A similar technique can be employed, in smaller animals, using an otoscope to visualise the larynx. An introducer is passed down the speculum into the trachea, the otoscope is removed and the endotracheal tube passed over the introducer and into the trachea. The introducer is then removed and the tube tied in place.

In all species it is advisable to administer 100% oxygen for 1-2 minutes before intubation, as this will usually maintain arterial oxygen saturation whilst intubation is performed. Monitor the animal with a pulse oxymeter during the intubation, so that attempts can be discontinued and oxygen administered if the animal becomes hypoxic ($pO_2 < 80\%$)

Circulatory function

To minimize the risk of circulatory failure, the cardiovascular system should be monitored during anaesthesia. Heart rate and rhythm can be monitored in most species, and in larger animals this can be done either by palpating a peripheral pulse,

or by use of an oesophageal stethoscope. Although it is not usually possible to palpate the peripheral pulse in small primates, the heartbeat can be detected by palpating the chest wall. However, since the heart rate often exceeds 200 bpm in many of these small animals, it is not possible to count the heart rate accurately.

The adequacy of the peripheral circulation can be assessed using the capillary refill time. The mucus membranes on the inside of the lip are blanched by pressing with a finger, and the refill time assessed when pressure is removed. The colour of the membranes should return to normal in less than a second. Assessment of the colour of the mucus membranes can also give some indication of problems associated with blood loss, cyanosis, and poor peripheral perfusion.

- On the body surface, the electrocardiograph (ECG) detects electrical changes that are caused by the sum of ion movements across the cell membranes of the cardiac cells. The actual shape of the ECG curve produced thereby depends on the relative orientation of the ECG electrodes in relation to the axis of the heart. Specific positions for these produce shapes that are named leads (I-III). For most applications in small animal anaesthesia, a lead II ECG is employed. If the ECG electrodes are positioned according to the described leads some diagnostic assessments can be made evaluating the shape and relation of single components of the ECG curve. However, during anaesthesia, the major use of the ECG is simply the detection of arrhythmias and conduction abnormalities (heart blocks). Presence of an ECG trace on the monitor does not necessarily correlate with heart pump function. In fact, cardiac arrest, the ECG trace may remain unchanged for several seconds. This phenomenon is called electro-mechanical dissociation (EMD)
- Blood pressure is measured on a routine basis. This is, however, mostly due to difficulties in measuring other cardiovascular variables such as cardiac output or peripheral perfusion, which could give more meaningful measurements of correct functioning of the system. Pressure relates to the radial tension within a vessel and is an indicator of vessel filling. Vessel diameter in the periphery, however, is very variable under clinical conditions and thereby a set amount of blood can produce variable degrees of vessel filling, and consequently of blood flow to the tissues.
 - Non-invasive blood pressure monitoring: This method rely on occluding an artery by application of external pressure around a limb or tail and then, gradually reducing it step by step to detect intra-vascular changes in blood flow turbulence or pulse. Correct positioning of the limb and the cuff are crucial for correct measurement. (i.e. a limb should neither be excessively flexed nor extended, and the cuff placed where an artery is detectable, and not over a joint!)
 - Invasive blood pressure monitoring: A cannula is introduced in to an artery and connected by way of a fluid-filled, non-compliant tubing, to a measuring device. The fluid-gas interface needs to be positioned at the level of the heart. This method is particularly useful when rapid changes in blood pressure are anticipated, when small blood pressure changes are detrimental to the animal, when frequent arterial blood samples are needed (blood gas analysis), or when the non-invasive technique is inaccurate.

Total blood volume is approximately 70 ml/kg of bodyweight in most mammals and loss of more than 15% can lead to signs of circulatory failure. In small animals, these volumes will be very small. It is therefore critically important to monitor blood loss. Setting up an intravenous infusion of fluid is need for supporting the circulation or treating cardiac arrest. Initially a balanced electrolyte solution should be given, at a rate of approximately 5-10 ml/kg/h, and if blood loss occurs, whole blood or plasma volume expanders (eg Haemacel) can be given. Whole blood can be collected from a donor animal and immediately mixed with acid-citrate-dextrose, at a rate of 1:4. Cross matching of blood is advisable, but in an emergency, an initial transfusion can usually be given safely using blood from another animal of the same species.

If intravenous administration of fluids is considered impractical or technically too demanding, then some circulatory support can be provided by administering intraperitoneal or subcutaneous electrolyte solutions. This is ineffective in cases of severe haemorrhage, but is of value in providing fluid supplementation post-operatively.

Monitoring depth of anaesthesia

Before starting a surgical or other painful procedure, it is essential to ensure that the animal is at an appropriate depth of anaesthesia. Too light causes experience of pain and moving during the procedure, too deep a risk of cardiopulmonary arrest and even death.

Reflexes disappear as the animal becomes deeper under anaesthesia in the following order;

- Palpebral reflex (blinking when the edge of the eyelids is lightly touched) is lost during the onset of light surgical anaesthesia.
- Pedal withdrawal reflex
- Corneal reflex

The most reliable method is to assess the pedal withdrawal reflex. Most surgical procedures can be carried out when the pedal withdrawal reflex is absent or barely detectable.

Monitoring of the respiratory and circulatory function during anaesthesia is also very helpful;

- At deep planes of anaesthesia respiratory rate and cardiovascular function decrease and cardiac arrest may occur shortly after reaching such a deep plane of anaesthesia
- Respiratory rate and heart rate increase by feeling pain.

V. Post-operative Care

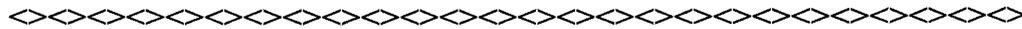
Recovery should be smooth, without excitement, or prolonged recumbency, and should be free of pain. Since all animals will require some degree of special attention in the post-operative period, it is preferable to provide a separate recovery area. This not only enables more appropriate environmental conditions to be maintained but also encourages individual attention and special nursing.

- The ambient temperature should be warmer than the animal's usual housing, since the thermoregulation may be impaired during recovery from anaesthesia. The temperature can gradually be reduced to the normal range as the animal regains normal activity. (achieved by using a purpose made of incubator or recovery pan)
- Provide suitable bedding. Sawdust and shavings are generally unsuitable, as they can clog or abrade the animal's eyes, nose and mouth. It is preferable to use towelling or synthetic sheepskin bedding.
- The recovery area should be quiet, with subdued lighting, but light levels should be adjustable to allow clinical assessment of the animal.
- The degree of nursing attentions provided in the recovery period should be tailored to suit the species concerned, since some respond positively to human contact, whereas others may find this attention stressful. Some handling is inevitable during the recovery period.
- Fluid therapy should be considered a routine requirement following surgical procedures. Many animals reduce their fluid intake post-operatively, and the consequent dehydration may contribute to post-operative distress, and increase morbidity and mortality. The normal fluid requirements of mammals are 40-80 ml/kg/24 h, and if the voluntary intake is inadequate, fluids can be supplemented either by hand feeding, or by subcutaneous, intraperitoneal, or intravenous administration.
- It is particularly important that good post-operative analgesia is provide, both for animal welfare reasons and because pain can prolong the effects of surgery. Whenever possible, attempts should be made to assess the degree of pain that is being experienced by the animal. This will enable selection of an appropriate analgesic, and ensure it is administered at an appropriate, effective dose, for a sufficient period.

Appendix

List of Anesthetic, Analgesic and Tranquilizer Drugs Frequently Used With the Common Laboratory Species.

Prepared by: Paul H. Bramson, DVM
Robert A. Wagner, VMD



1. Rodents	Pages 3 - 8
2. Rabbits	Pages 9 - 12
3. Dogs and Cats	Pages 13 - 17
4. Primates	Pages 18 - 21
5. Pigs	Pages 22 - 25

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Primates: Chemical Restraint and Anesthetic Agents

Agent	Dosage	Comments
Acepromazine	0.5-1.0 mg/kg PO, SC, IM	Pre-anesthetic; tranquilizer
Atipamizole (Antisedan)	0.15-0.30 mg/kg IV	Medetomidine reversal
Atropine	0.04 mg/kg SC, IM, IV	Pre-anesthetic; reduces salivation and bradycardia.
Diazepam (Valium)	0.5-1.0 mg/kg PO	Sedative; give in small amount of food or drink 30-60 min. prior to anesthesia; prolongs recovery.
	0.25-0.50 mg/kg IM, IV	Reduces seizures; muscle relaxer during anesthesia.
Fentanyl	5-10 ug/kg IV bolus	Use prior to Isoflurane anesthesia
	10-25 ug/kg/hr. continuous infusion IV	Use with Isoflurane anesthesia
Glycopyrrolate (Robinul)	0.005-0.010 mg/kg IM, SC	Pre-anesthetic; reduces salivation and bradycardia. Lasts longer than atropine.
Ketamine (Ketaset, Vetalar)	10-15 mg/kg IM	Medium-sized primates; 20 minutes of immobilization.
	25-30 mg/kg IM	Surgical anesthesia for smaller and New World primates; 20 min. duration; for minor procedures only.
Ketamine(K)/ Acepromazine(A)	(K) 4 mg/kg + (A) 0.04 mg/kg IM	Anesthesia for minor procedures only.
Ketamine(K)/ Diazepam(D)	(K) 15 mg/kg + (D) 1.0 mg/kg IM	Anesthesia for minor procedures only.

Primates: Restraint and Anesthesia (cont.)

Agent	Dosage	Comments
Ketamine(K)/ Medetomidine(M)	(K) 5.0-7.5 mg/kg + (M) 0.033-0.075 mg/kg IM	Anesthesia; use higher doses for smaller primates; for minor procedures only.
Ketamine(K)/ Xylazine(X)	(K) 10 mg/kg + (X) 0.5 mg/kg IM	Anesthesia for minor procedures only.
Medetomidine (Domitor)	0.05-0.10 mg/kg PO 0.10 mg/kg SC, IM	Induction; can be followed by Ketamine. Dosage for Squirrel Monkeys
Naloxone	0.01-0.05 mg/kg IM, IV	Narcotic reversal
Propofol	2.5-5.0 mg/kg IV bolus, followed by infusion of 0.3-0.4 mg/kg/min.	Intubation and ventilatory support suggested.
Thiopental (Pentothal)	25 mg/kg IV to effect	Anesthesia
Tiletamine/Zolazepam (Telazol)	2-6 mg/kg IM (1-20 mg/kg IM)	Anesthesia; cataleptoid. For species other than Macaques wide range of doses.

Primates: Analgesics **Categories: 1. Mild pain**
2. Moderate pain
3. Severe pain

Agent	Dosage	Comments
Acetaminophen (Tylenol)	5-10 mg/kg PO q6h.	Analgesic/ NSAID; anti-pyretic.
Acetylsalicylic acid (Aspirin, Ecotrin)	5-20 mg/kg PO q4-6h. 100 mg/kg PO SID 325 mg (5 gr.) PO QID	Analgesic/ NSAID; anti-pyretic.

Primates: Analgesics (cont.)

Agent	Dosage	Comments
Buprenorphine (Buprenex)	0.01 mg/kg IM, IV q12h. 0.005-0.01 mg/kg IM, IV q6-12h.	Analgesia (2); most useful of the opioid agonist-antagonists.
Butorphanol (Torbugesic, Stadol)	0.1-0.2 mg/kg IM q12-48h. 0.01 mg/kg IV q3-4h.	Analgesia (2); Do Not give during anesthesia due to Respiratory Depression.
Carprofen (Rimadyl)	2-4 mg/kg PO, SC q12-24h.	Analgesic (1+2)/ NSAID
Fentanyl patch (Duragesic)	4-8 ug/kg/hr., change patch q72h.	Analgesic (2+3); do not cut patch.
Flunixin meglumine (Banamine)	0.3-1.0 mg/kg SC, IV, IM q12-24h.	Analgesic (1+2)/ NSAID
Ibuprofen (Advil)	20 mg/kg/day PO 1% solution, sub-gingival irrigation.	Analgesic (1)/ NSAID Periodontitis
Ketoprofen (Ketofen)	5 mg/kg IM q6h.	Analgesic (2)/ NSAID
Ketorolac (Toradol)	15-30 mg/animal IM, PO	Macaques, baboons; Analgesic (2)/ NSAID
Meperidine (Demerol)	2-4 mg/kg IM q3-4h.	Analgesic (2+3); Narcotic; sudden death reported in healthy animals; Squirrel monkeys require 8 mg/kg.
Midazolam (Versed)	0.1-0.5 mg/kg IM	In lemurs prevents Ketamine-induced seizures.
Morphine	1-2 mg/kg PO, SC, IM, IV q4h.	Analgesic (2+3); Narcotic.

Primates: Analgesics (cont.)

Agent	Dosage	Comments
Nalbuphine (Nubain)	0.5 mg/kg IM, IV q3-6h.	Analgesic (2+3)
Oxymorphone	0.03-0.2 mg/kg SC, IM, IV q6-12h. [0.075 mg/kg q6h.: New World Primates] [0.15 mg/kg q6h.: Old World Primates]	Analgesic (2+3)

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