

# Pain assessment, alleviation and avoidance in laboratory animals

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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)".

In order to provide effective analgesia, it is essential that we have a good knowledge and understanding of animal pain:

- we need to know when pain might occur, how long it might last and how well it will respond to therapy;
- we need to consider the advantages and disadvantages of the various methods of managing pain, and how we can best apply these in different situations.
- for optimal pain management we need to recognise the presence of pain and assess its severity; and
- more fundamentally, we need to be certain that pain occurs in animals; that it can result in suffering, in a similar way to pain in man; and so become convinced that its avoidance and alleviation need to be given a high priority.

## Do animals experience pain?

Although it is widely accepted that animals experience pain, it is important that we establish a basis for this assumption. There can be no doubt that the ability to detect damaging or potentially damaging stimuli, for example excess heat or mechanical pressure, is present in many animal species. Possession of this detection system does not, in itself, mean that animals experience pain. Pain in man has both a sensory and an emotional component. Without interpretation by the brain of the sensory information arriving from peripheral nerves, the characteristic unpleasant and distressing nature of pain is not appreciated. The initial processing of information arising in the peripheral detection system, which relates to potentially damaging stimuli, is termed nociception. These processes are virtually identical in animals and man, but interpretation of this information centrally, in the cerebral cortex, is needed for pain to be experienced.

Whether animals possess the same, or a similar capacity as man to experience emotions such as pain has been extensively debated for centuries. The main reason for the continued debate is that it is impossible to investigate such emotional states directly - we can only draw inferences from other, indirect, measures, such as investigation of behavioural responses. Scientific support for the belief that animals can suffer often consists simply of drawing parallels in animal and human neuroanatomy, and making the assertion that animals "are given the benefit of the doubt". When comparing the central nervous system structures believed to be associated with pain perception, or at least with the unpleasant aspect of pain, it is likely that the pre-frontal cortex has an important role. In man, pre-frontal lobotomy was used as a treatment for some psychiatric disorders. Patients who had undergone this procedure still responded to painful stimuli by reflex movements, but expressed no concern about their pain - it was no longer considered unpleasant. Most animal species have relatively small areas of pre-frontal cortex, and this has led to the suggestion that pain in animals is comparable to that experienced by lobotomised humans (Melzack and Dennis, 1980; Bermond, 1997). This assumes that absolute size of the pre-frontal cortex will determine the capacity for pain perception, but it may be that other areas of the brain carry out a similar role in other species. What is clear, however, is that animals do not behave in simple, reflex ways, in circumstances that would cause pain in man.

## Animals and their response to pain

Aside from immediate avoidance or defence reactions, such as struggling or biting when an injured limb is handled, animals show a range of more subtle behavioural responses to pain. Animals can be trained to perform complex tasks to avoid brief painful stimuli, and more complex studies have shown that animals can choose to self-administer analgesics when they develop chronic painful conditions (Colpaert, 1987). The response to an analgesic has often been used to determine whether a behaviour was pain related, and although it can become a circular argument (animal pain behaviour is behaviour modified by analgesic drugs, which are drugs that alleviate pain), it provides some useful information when developing pain assessment schemes for animals.

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The development of assessment schemes is of central importance to our understanding and appreciation of animal pain. If we cannot assess pain, we cannot manage it effectively, and it is likely that a failure to appreciate the severity of pain in individual animals is the single most important factor in the apparent underuse of analgesics in animals. Most of us expect to be able to recognise pain in animals, and we develop clear ideas concerning responses to acute pain. Unfortunately, we retain a level of anthropomorphism, which leads us to expect animals in pain to behave in the same way as humans in pain. Animals in pain could be expected to behave in different ways depending upon the site, severity and type of pain, but we should also expect them to behave in a species-specific way. Some species, especially those which may expect support from others, may show very obvious pain-related behaviour. In other species, expressing such overt behaviour would simply alert predators that they were less fit and hence easy prey. If overt pain-related behaviour is expressed, then the animal may mask this behaviour when it is aware it is being observed.

Animals may also change their responses when in a familiar, secure environment, and express less pain-related behaviour than when in an unfamiliar environment – for example when removed from their cage for examination.

It is important that we examine our preconceptions about pain behaviour critically and try to establish which clinical signs indicate the presence of pain in animals. These clinical signs are of course likely to vary in different species and with different clinical conditions. Although our ability to recognise pain in animals remains poor, adopting a critical approach has enabled pain scoring systems for dogs, cats, horses, sheep, calves and small rodents to be developed (see below). As further studies progress, it should be possible to devise systems of assessment that can be introduced successfully into most research animal units. One important point to note is that many of these schemes are attempting to differentiate small gradations in the animals' sensation of pain. Recognising obvious clinical signs of marked pain in some species such as the dog and cat is not difficult, and should result in use of appropriate analgesic therapy.

#### **When could pain occur?**

It does not seem unreasonable to assume that since the peripheral mechanisms for detection of potentially painful stimuli are similar in animals and man, and the mechanisms for processing these signals are remarkably similar, then the circumstances that could give rise to pain will also be similar. Clearly, we must also give careful consideration to differences in anatomy, and differences in the natural environment of particular species, but broad similarities are likely to exist. If this is so, then it should influence our decision-making. At present, in veterinary clinical practice, analgesics are widely used to control pain in two groups of animals – those which have undergone

surgery or have suffered traumatic injuries, and those with acute or chronic arthritis. In research animal facilities, alleviation of post-operative pain probably represents the greatest area of analgesic use. In man, there are a range of other circumstances in which pain can occur – for example, disease processes with a marked inflammatory component, or some types of neoplasia. When these conditions are modelled in laboratory species, in order to develop novel therapies or study underlying mechanisms of these disease processes, use of analgesics may be precluded because of interactions with the research protocol. It is important that these potential interactions are addressed logically, and this issue is discussed further below. The potential interaction between analgesic therapy and research protocols also arises when dealing with post-surgical pain, but even when this is not seen as a significant issue, other reasons for withholding analgesics may be advanced.

- *Alleviation of post-operative pain will result in the animal injuring itself.* Provided that surgery has been carried out competently, administration of analgesics, which allow resumption of normal activity, rarely results in problems associated with the removal of pain's protective function. Claims that analgesic administration results in skin suture removal are unsubstantiated, and contrary to findings in our laboratory. In our institute, administration of analgesics to laboratory animals after a wide variety of surgical procedures has not resulted in any adverse clinical effects.
- *Analgesic drugs have undesirable side-effects such as respiratory depression.* The side-effects of opiates in animals are generally less marked than in humans and should rarely be a significant consideration when planning a post-operative care regimen.
- *We don't know the appropriate dose rates and dosage regimens.* This is primarily a problem of poor dissemination of existing information. Virtually every available analgesic drug has undergone extensive testing in animals. Dose rates are therefore available for a range of drugs in many common laboratory animal species. It is occasionally difficult to extrapolate available dose rates from one species to another and to translate dose rates that are effective in experimental analgesiometry into dose rates which are appropriate for clinical use. Nevertheless, in most instances a reasonable guide as to a suitable, and safe, dose rate can be obtained.
- *Pain-relieving drugs might adversely affect the results of an experiment.* Although there will be occasions when the use of one or other type of analgesic is contra-indicated, it is extremely unlikely that there will be no suitable analgesic that could be administered. More often, the reluctance to administer analgesics is based upon the misconceived idea that the use of any additional

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medication in an experimental animal is undesirable. The influence of analgesic administration in a research protocol should be considered in the context of the overall response of the animal to anaesthesia and surgery. The responses to surgical stress may overshadow any possible adverse interactions associated with analgesic administration. An additional consideration is that many arrangements for intra-operative care fail to control variables such as body temperature, respiratory function and blood pressure. It seems illogical to assume that changes in the function of the cardiovascular or respiratory systems are unimportant, but that administration of an analgesic will be of overriding significance. It should be considered an ethical responsibility of a research worker to provide a reasoned, scientific justification if analgesic drugs are to be withheld. It is also important to realise that the presence of pain can produce a range of undesirable physiological changes, which may radically alter the rate of recovery from surgical procedures. In animals, post-surgical pain can reduce food and water consumption, interfere with normal respiration (for example after thoracotomy), and reduce a whole range of "self-maintenance" behaviours. The immobility caused by pain can lead to muscle spasm, can cause atrophy of areas, and can slow healing. Prolonged immobility can also cause pressure sores, urine scalding, faeces soiling and can greatly complicate animal care routines.

Finally, there may be legal constraints concerning analgesic use that can restrict their administration. In many countries, the use of the majority of opioids is controlled by legislation. Complying with this legislation often requires careful record keeping of the purchase, storage and dispensing of opioids and may restrict the persons who are able to dispense and administer these substances. In some countries the degree of record keeping required can act as a strong disincentive. Legislative control, together with genuine safety concerns may also limit the dispensing of this class of analgesics for use by investigators or technicians .

### **Progress in pain assessment**

If we are going to control pain effectively, we need to assess it accurately. The difficulty in assessing pain often results in one of the following approaches being adopted:

- analgesics are withheld because the animal shows no obvious signs of pain (in other words, it does not behave in a similar way to a human experiencing pain); or
- it is assumed that since a human who had undergone a similar procedure would require analgesics, the animal is in need of pain relief, and analgesics are administered.

In the first case, animals that are almost certainly in pain will not receive adequate analgesia. In the second case, since no proper assessment of the degree of pain has been made, it is a matter of chance whether an appropriate degree of pain relief is provided. It is important to emphasise that, in our experience, adopting the latter approach and administering an initial dose of analgesic is almost invariably beneficial, and rarely causes significant clinical side effects. Administering repeated doses of analgesics to animals which are not experiencing pain may, however, be detrimental – for example the drug may depress appetite and so delay recovery (Flecknell and Liles, 1992). Clearly it is preferable to try to assess pain, and adjust the analgesic regimen according to this assessment.

When considering how we might assess pain in animals, considerable parallels can be drawn with the situation in human infants. The most widely used techniques have been pain-scoring systems based upon criteria such as crying, facial expression, posture and behaviour (McGrath and Unruh, 1989). An experienced observer then scored these behaviours. This approach has been used in a wide range of species, mainly to assess post-surgical pain, with some success. All of the pain-scoring techniques used are highly subjective, and standardising scores between observers remains a problem.

In laboratory animals, a number of different approaches have been used to assess pain or distress. An initial assessment scheme, using a numerical scale, was proposed by Morton and Griffiths (1985). This paper influenced a large number of other groups, who modified the original hypothesis, but retained the central notion of identifying pain-specific behaviours, and rating them in some way (e.g., AVTRW, 1986; LASA, 1990; Flecknell and Liles, 1991). Loss of appetite and reduction in body weight have been noted in rodents post-operatively (Morton and Griffiths, 1985; Wright *et al.*, 1985) and these variables have been studied in rats as potential means of assessing the degree of post-operative pain, and comparing the efficacy of different analgesic regimens (e.g., Flecknell and Liles, 1991; Flecknell and Liles, 1992; Liles and Flecknell, 1992, 1993a, 1993b). Measures of food and water consumption and body weight are, of course, retrospective, and do not allow the analgesic regimen to be modified to meet the requirements of the individual animal. They have, however, enabled broad assessments of analgesic efficacy to be made. A number of recent studies have used more detailed behavioural analyses to assess pain, and further development of this approach should lead to practically useful scoring systems. In summary, whether a scoring system is used or not, pain assessment will be facilitated by:

- a good knowledge of the species-specific behaviours of the animal being assessed;
- a knowledge and comparison of the individual animal's behaviour before and after the onset of pain (e.g., pre- and post-operatively);

- the use of palpation or manipulation of the affected area and assessment of the responses obtained;
- examination of the level of function of the affected area e.g., leg use following injury or limb surgery, together with a knowledge of any mechanical interference with function.
- the use of analgesic regimens or dose rates that have been shown to be effective in controlled clinical studies, and evaluation of the change in behaviour this brings about; and
- a knowledge of the non-specific effects of any analgesic, anaesthetic or other drugs that have been administered.

### **Pain relief**

Leaving aside the problems of pain assessment, it is not unreasonable to assume that analgesic therapies shown to be effective in man are likely to also be effective in animals. Analgesics can be broadly divided into two groups, the opioids or narcotic analgesics and the non-steroidal anti-inflammatory drugs (NSAID) such as aspirin. Local anaesthetics can also be used to provide post-operative pain relief by blocking all sensation from the affected area. Suggested dose rates of analgesics are given in Tables 1-2.

### **Clinical use of analgesics**

When formulating an analgesic regimen for a particular animal, several factors need to be considered.

- What is the likely severity of pain, and what is its anticipated duration?
- Which drug or drugs should be administered, and at what dose rates?
- Are there any special factors that will influence the choice of analgesic, for example, the species of animal, any potential interactions with the particular research project, or any particular features of the current condition and the type of pain?
- What facilities are available for management of the animal? What level of nursing care and monitoring of the animal is available? Can staff attend throughout a 24 hour period? Are there facilities for continuous infusion of analgesics?

### **Timing of analgesic administration**

Although an animal may be unconscious during surgery, the peripheral nerves carrying nociceptive information are still active. This information arriving in the central nervous system produces changes that increase the perception of pain once the animal has regained consciousness. To be

most effective, analgesics should prevent the noxious stimuli from reaching the central nervous system. Reducing or eliminating peripheral inflammation, which in itself increases input into the CNS, and so aggravates central hypersensitivity, is also important. Therefore:

- administer analgesics pre-operatively whenever possible;
- administer additional analgesics in the post-operative period, recognising that pain will be more easily controlled if pre-emptive analgesia has been used;
- use of pre-emptive analgesia will often reduce the dose of anaesthetic drugs required, so reducing anaesthetic side-effects and reducing risks associated with anaesthesia;
- if analgesics cannot be given pre-emptively, administer them as soon as is practicable. The longer pain is established, the greater will be the degree of central hypersensitivity, and the more difficult pain management becomes.

### **Multi-modal pain therapy**

Since pain arises because of activation of a large number of different mechanisms, the most effective pain relief is provided by administering drugs from several different classes of analgesics, each acting on different parts of the pain system.

This concept is easy to apply in clinical practice, for example, by combining the use of opioids with NSAIDs. The opioid acts centrally to limit the input of nociceptive information into the CNS and so reduces central hypersensitivity. In contrast, the NSAID acts both centrally, to limit the central changes induced by the nociceptive information that does get through, and also peripherally to decrease inflammation during and after surgery, and thus limits the nociceptive information entering the CNS as a result of the inflammation.

### **Anaesthesia and analgesia**

Anaesthesia does not necessarily equate with analgesia. General anaesthesia produces loss of consciousness, so the animal cannot perceive pain, but in unconscious animals, noxious stimuli will still be transmitted to the CNS. Although these noxious stimuli will not be consciously perceived as pain, central hypersensitivity will still develop, and so post-operative pain perception will be heightened. Some anaesthetic agents do have analgesic effects (e.g., ketamine and  $\alpha_2$  adrenoreceptor agonists such as medetomidine) and analgesics may be used as part of the analgesic regimen (e.g., opioids such as fentanyl). These factors, together with the need to use analgesics as soon as possible, and the advantages of using multiple classes of analgesics, should be taken into account when

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planning a peri-operative analgesic protocol.

### **Pain relief – practical considerations**

Most of the opioid (narcotic) analgesics have a relatively short duration of action. Maintenance of effective analgesia with, for example, pethidine, may require repeated administration every one to three hours, depending upon the species. Continuation of such a regime overnight can cause practical problems. One method of avoiding this difficulty is to use buprenorphine as the analgesic, since there is good evidence in humans and a number of animal species that it has a duration of action of six to twelve hours. An alternative approach is to adopt the well-established human clinical technique of administering analgesics as a continuous infusion.

NSAIDs tend to have long durations of action, and the newer agents (e.g., carprofen, ketoprofen, and meloxicam) are effective in controlling moderate post-surgical pain in many circumstances.

Epidural and intrathecal opioids have been shown to have a prolonged effect in man and to provide effective analgesia, and clinical studies have indicated that the technique can be used in a number of species. The necessary techniques of epidural or intrathecal injection have been described in the rabbit (Kero, Thomasson and Soppi, 1981; Hughes, Doherty and Charman, 1993). In larger species such as the cat, dog, sheep and pig, descriptions of the injection technique can be found in most veterinary anaesthesia texts and a number of other publications (e.g., Thurmon *et al.*, 1996)

The need for repeated injections of analgesics is time consuming and may be distressing to the animal, particularly smaller species, which require firm physical restraint to enable an injection to be given safely and effectively. Analgesics can be added to food or water, but some animals eat and drink relatively infrequently, or may only do so in the dark phase of their photoperiod. In addition, food and water intake may be depressed following surgery, and this, coupled with wide individual variation in consumption, makes routine application of the technique difficult. Finally, the high first-pass liver metabolism of opioids administered by the oral route requires that high dose rates are given, and this can represent a significant cost if all of the animals' drinking water or food is medicated. Administration of small quantities of medicated food does not avoid the need for repeated attendance overnight, but does remove the need for repeated subcutaneous or intramuscular injections in small rodents. Provision of analgesia with buprenorphine in flavoured gelatin "Buprenorphine Jello", (Pekow, 1992) seems to be an effective means of providing post-operative pain relief. In our laboratory, we have noted that rats are initially cautious of jelly pellets, but once one pellet has been consumed, subsequent pellets are eaten as soon as they are offered. It is therefore advisable to commence

administering pellets, which do not contain analgesic, two to three days before surgery. After surgery, analgesic-containing jelly can be given. The flavoured gelatin used is domestic fruit-flavoured jelly, reconstituted at double the recommended strength. We have also recently used meloxicam (which is available as a palatable oral preparation) for post-surgical pain relief in rats.

Administration of opioids by any route can be associated with the development of respiratory depression. It must be emphasised that this is rarely of clinical significance in animals unless high doses of pure  $\mu$  agonists (e.g., fentanyl) are used. If respiratory depression occurs, it can be treated by the administration of the opiate antagonist drug, naloxone. Administration of naloxone will also reverse the analgesic effects of the opioid and it may be preferable to correct the respiratory depression by the use of doxapram. Alternatively, if a  $\mu$  agonist opioid such as morphine or fentanyl has been used, the respiratory depression can be reversed using nalbuphine or butorphanol, and some analgesia maintained because of the action of these latter two agents at kappa receptors. Repeated administration of these agents may be required, and the animal should be observed carefully for several hours to ensure adequate respiratory function is maintained.

Gastric distension associated with pica has been reported in rats given large doses (0.5mg/kg s/c) of buprenorphine, although effects in rats receiving a lower dose (0.05mg/kg) were minimal (Clark *et al.*, 1997). There are also reports of gastric obstruction occurring after use of buprenorphine. It seems likely that this effect varies with the strain of rat and the anaesthetic regimen used. If problems are encountered, then alternative analgesics should be used.

### **Additional considerations in pain relief**

Although the use of analgesic drugs remains the most important technique for reducing post-operative pain, the use of these drugs must be integrated into a total scheme for peri-operative care.

Including an analgesic drug in any pre-anaesthetic medication can provide pain relief in the immediate recovery period.

If a neuroleptanalgesic combination has been used to produce anaesthesia, it can be reversed by the use of buprenorphine, nalbuphine or butorphanol, rather than with naloxone. These agents have been shown not only to reverse the respiratory depressant effects of opioids such as fentanyl but, in contrast to naloxone, to provide effective prolonged analgesia.

The expertise of the surgeon can also greatly influence the degree of post-operative pain. Good surgical technique, which minimises tissue trauma and the

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prevention of tension on suture lines, can considerably reduce post-operative pain. The use of bandages to pad and protect traumatised tissue must not be overlooked and forms an essential adjunct to the use of analgesic drugs.

Aside from measures directed towards alleviating or preventing pain, it is important to consider the overall care of the animal and the prevention of distress. Distress is used in this context to describe conditions which are not in themselves painful, but which are unpleasant and which the animal would normally choose to avoid. For example, recovering from anaesthesia on wet, uncomfortable bedding in a cold, unfamiliar environment would be likely to cause distress to many animals. It is essential to consider the methods described for the control of pain in conjunction with good post-operative care.

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