

# **ANALGESIA OF LABORATORY ANIMALS**

**ANZCCART WORKSHOP**

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**Notes on pain, pain assessment in animals, analgesics,  
pain relief and research**

by

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## **Introduction**

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 also need to consider the advantages and disadvantages of the various methods of managing pain, and the how we can best apply these in different situations. If we are to manage pain relief optimally, and monitor the efficacy of our therapy, then we will need to recognise the presence of pain and assess its severity. When developing our understanding of this area we will also need some information about the basic mechanisms involved in pain perception. 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. This workshop will try to address some of these issues. It is important to make clear at the outset that our knowledge of animal pain, and its assessment and alleviation, is still very limited. For many years, the information on analgesic agents and their use in animals has been very limited, and attempts at pain assessment were rudimentary. In recent years there has been a rapid increase in information, but much of it has yet to be applied to in laboratory animals. Despite the availability of analgesic agents, our use of them remains low in comparison to their use in man. The possible reasons for this are discussed below, together with a consideration of some of the more fundamental issues concerning the nature of pain perception in animals.

## **Animal pain and analgesic use**

Most persons involved with animals of any type would have no hesitation in stating that animals experience pain. On reflection, they might add that the experience might not be exactly the same as the pain they might experience themselves, but nevertheless would have no doubt that it was "Pain". There is little data concerning attitudes to animal pain in laboratory animal facilities (although two studies are currently in progress in the UK), and the most recent information of this type comes from surveys of the veterinary profession in the UK and Canada. These questionnaires established that the majority of respondents considered animals to experience pain in a range of circumstances, for example following surgery (Dohoo and Dohoo, 1996; Capner et al, 1997). However, the information obtained also demonstrated that analgesics were not used routinely by veterinarians. If the veterinary clinicians surveyed believed that the animals they treated experienced pain, why was their use of analgesics so low, compared to best practice in human patients? Despite increased availability of analgesic agents for use in animals, only 50% of dogs and cats received analgesics after ovariohysterectomy, and only 23% of small mammals after major surgery (Capner et al, 1997). Use in medical conditions which could be considered likely to cause pain, for example neoplasia, mastitis and otitis externa is likely to be considerably lower. It seems appropriate then, to examine some of the assumptions we make about animal pain, and to assess whether these could influence decisions concerning the use of analgesics.

## **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 is recognised as having 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". The interpretation of this information centrally results in the experience of pain. Animals and humans both possess nociceptors, and these receptors, and the types of nerve fibres that connect them to the central nervous system are virtually identical in animals and man. The processing of this information in the spinal cord and lower parts of the brain is also very similar, and potential differences primarily arise when the information reaches the cerebral cortex. 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 are 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. Some philosophers have firmly asserted that animals cannot experience pain - the most often quoted is Descartes, who stated "The greatest of all the prejudices we have retained from our infancy is that of believing that the beasts think". Descartes asserted that since animals had no capacity for reasoning, they could have no perception of pain, and that their reactions to stimuli that would cause pain in man were simply the responses of automatons. Although there have been a number of different responses to Descartes' ideas, that of Jeremy Bentham, the 18th century utilitarian philosopher, is most frequently cited "The question is not can they reason? Nor can they talk? But can they suffer?". Bentham's view that animals can suffer is now widely held, and underpins the legislation controlling the use of laboratory animals in a number of countries. 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 (Preuss, 1995). 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. 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 under-use of analgesics discussed earlier. 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 when in an unfamiliar environment, for example when removed from their cage for examination. It is important, then, 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. It is important not simply to assume that conditions that are painful in man will be painful in animals, since the choice of analgesic should be influenced by the degree of pain that is actually present. If inappropriate use is made of a potent analgesic, then the undesirable side-effects of the agent may out-weigh any potential pain alleviating effects. To determine the degree of pain that is present, and so choose an appropriate analgesic regimen, some form of assessment is required. Without a scheme of assessment, it is necessary to assume that the degree of pain present will be identical in humans and animals in similar circumstances. A consideration of the differences in anatomy, posture and behaviour between animals and man illustrates that this assumption is unlikely to be correct. Furthermore, in order to provide effective pain relief for as long as required, if no assessment scheme is used then it is necessary to assume that the duration of pain, for example following a particular surgical procedure, will be identical in animals and man. It will also be necessary to assume that the rate of decrease in the severity of the pain is also the same. Even if these assumptions were to be true, it is also necessary to assume that all animals will experience the same level of pain. In man, it is well established that different individuals have different analgesic requirements after apparently identical surgical procedures (Alexander & Hill, 1987). In man, the dose of analgesic administered, and the frequency and duration of treatment can be adjusted by assessing pain in each individual patient. In animals, it seems reasonable to assume that effective pain relief can be achieved only by making a similar assessment. Selection of an arbitrary initial dose of analgesic is unlikely to prove uniformly effective. The

response to a particular dose of an analgesic has been shown to vary considerably between animals of different strains, ages and sexes (Frommel and Joye, 1964; Katz, 1980; Moskowitz et al, 1985). So selection of a particular dose regimen can result in over-dosage of some animals, and provision of inadequate analgesia for others. It is therefore of fundamental importance that accurate methods of assessment of pain and distress are developed, so that analgesic treatment can be tailored to suit the needs of each individual patient. Although our ability to recognise pain in animals remains poor, adopting a critical approach has enabled pain scoring systems in 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 interactions 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 certain circumstances, for example after major orthopaedic surgery, additional measures to protect and support the operative site may be required, but this is preferable to allowing an animal to experience unrelieved pain. All that is required in these circumstances is to temporarily reduce the animal's cage or pen size, or to provide additional external fixation or support for the wound. It must be emphasised that these measures are very rarely necessary,

and 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 species (Flecknell, 1984; Liles & Flecknell, 1992). It is occasionally difficult to extrapolate available dose rates from one species to another and to translate dose rates that are effective in experimental analgesiology 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 usually, the reluctance to administer analgesics is based upon the misconceived idea that the use of any additional 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 realize that the presence of pain can produce a range of undesirable physiological changes, which may radically alter the rate of recovery from surgical procedures (Keeri-Szanto, 1983). 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 result 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 (eg The Misuse of Drugs Act in the UK). 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**

As discussed earlier, 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:

- a) 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)
- b) 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 which 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 (Flecknell, 1994). 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 (Liles, 1992). Clearly it is preferable to try to assess pain, and adjust the analgesic regimen according to this assessment.

### **Assessment of acute pain responses - analgesiometry**

In addition to attempting to assess the severity of pain in clinical situations, the responses to a sudden, acute painful stimulus is often used to determine the efficacy of different analgesics. Since a number of analgesics are also sedative agents, it is often necessary to assess both analgesia and sedation. The majority of these investigations have been carried out in rodents, and use mechanical, thermal or electrical stimuli to produce a brief painful stimuli. Most studies are designed in such a way that the animal can terminate the stimulus. The various techniques used in rodents has been reviewed (Flecknell, 1984; Liles and Flecknell, 1992), and these systems have been modified for use in larger species. These assessment methods enable a determination of the analgesic potency of different drugs, but the dose rates required vary depending upon the test and the analgesic used. NSAIDs are generally relatively ineffective, and the test systems used require some modification when assessing this class of analgesics. This relative lack of efficacy in response to acute brief noxious stimuli, in comparison with opioids, is sometimes misinterpreted as showing that NSAIDs are therefore unlikely to be effective in controlling clinical pain. This is clearly not the case. It is also difficult to relate the dose rates which are effective in these test systems with those which are needed to control clinical pain. In some instances this can lead to relatively high dose rates of analgesics being recommended for clinical use, but these are usually revised once clinical studies have been carried out.

### **Assessment of clinical pain**

Numerous different methods of assessing pain have been developed in man, and attempts have been made to apply some of these to animals. The use of objective measures, such as heart rate, respiratory rate and temperature are an unreliable

guide to the presence of pain (Conzemius, 1997), as are clinicopathological measurements of humoral factors such as epinephrine (adrenaline), norepinephrine (noradrenaline) and cortisol. A major problem in interpreting the significance of these changes is the influence of surgery and anaesthesia, which markedly alter many of these variables, even in patients which are pain free (Kehlet, 1989). The surgical stress response occurs in all patients, and although it can be reduced by intra-operative use of opioids, it occurs even in patients who receive a high level of post-operative pain control. In man, catecholamine and cortisol responses have shown to be poorly correlated with post-operative pain scores (Murrin and Rosen, 1985). Use of these variables in animals has the same constraints. Although catecholamine rises have been demonstrated in cats (Benson et al, 1991) and dogs (Popilskis, et al. , 1993), and cortisol response shown to be less following thoracotomy and epidural morphine than intravenous morphine (Popilskis, et al. , 1993), lack of appropriate controls and influence of surgical stress limit the significance that can be attached to these studies. Despite these reservations, studies such as those of Popilskis et al, (Popilskis, et al. , 1993) which correlate both subjective pain scores and endocrine responses, advance a persuasive case of the validity of pain scoring. Nevertheless, the difficulties highlighted by studies in man suggest that biochemical indices are unlikely to provide a reliable objective method of pain assessment in animals. These measures may be useful when integrated into a pain scoring system, but since they may be influenced by so many factors other than pain, they are of limited use as predictors of pain severity when used alone.

When considering how we might assess pain in animals, considerable parallels can be drawn with the situation in human infants. In adult humans, the ability to provide direct verbal communication, to complete pain questionnaires or scoring systems, or to directly manage analgesic dosage using patient controlled analgesia systems allows reasonably reliable estimates to be made of the degree of pain and the efficacy of pain control. In young human infants, written and verbal communication is not possible, nevertheless extrapolation from adult humans, coupled with objective demonstrations of the adverse effects of surgical stress, has led to a huge increase in interest in providing pain relief to these patients (Anand, 1987; Anand, 1990). The approaches used in human infants may therefore provide a framework for animal pain assessment. The most widely used techniques have been pain scoring systems based upon criteria such as crying, facial expression, posture and behaviour (McGrath & Unruh, 1989). These behaviours were then scored by an experienced observer. The pain scales used have been either simple descriptive scales, numerical rating scales, visual analogue scales and multifactorial pain scales. These have all been adapted for use in animals, and they are described in more detail below. The visual analogue scale (VAS) consists of a 100mm line, labelled at one end "no pain" and at the other "Excruciating or unbearable pain", or some similar wording (Murrin and Rosen, 1985). The clinician assessing the animal places a mark on the line to indicate the amount of pain they believe the animal to be suffering. The distance from the "no pain" end of the line (in mm) is the pain score. The numerical rating scale (NRS) is similar, but the observer assigns a numerical score for pain intensity rather than placing a mark on a line. Typically, a scale of 0 to 10 is used. The simple descriptive scale (SDS) consists of four or five expressions used to describe various levels of pain intensity (no pain, mild pain, moderate pain or severe pain). Each expression is assigned an index value, which becomes the pain score for the animal. The multifactorial pain scale (MFPS) is usually a composite of a number of SDS values relating to particular aspects of behaviour that may be associated with pain. The performance of these scales for the assessment of pain in

both humans and animals has been investigated. It has been found that the SDS is less sensitive than the VAS or the NRS (Scott, 1976). Good agreement has been found between a VAS and a NRS when assessing lameness in sheep, but with the VAS being more sensitive (Welsh, 1993). Similar findings were obtained for the assessment of post-operative pain in dogs (Lascelles et al 1995). Comparisons of inter-observer variability using these scales has shown the agreement between observers using the SDS to be reasonable when assessing post-operative pain in dogs (Holton, 1998), and the differences between two observers scoring lameness in sheep using the VAS or NRS were not significant (Welsh, 1993). However, it has been suggested that the NRS may be the more suitable scale for assessing pain in a clinical setting, where a single knowledgeable person is responsible for pain management of the animal from before surgery into the post-operative period. It is possible that development of a multidimensional pain scoring system may improve pain assessment techniques (Reid and Nolan - work in progress). All of these pain scoring techniques rely primarily on behavioural signs, and interpretation of these is highly subjective. Detailed behavioural observations have been used to try to assess pain in both small laboratory mammals and farm animals. Studies of the effects of tail docking and castration in lambs (Wood, et al, 1991) and castration in piglets (McGlone & Hellman, 1988) used a series of well-defined behavioural parameters to compare the effects of these husbandry procedures with and without the use of local anaesthetic. Control groups which underwent handling but no other procedure were also included. The behavioural analysis of lambs subjected to docking and castration showed a clear difference associated with the use of local anaesthetic, with animals behaving in a manner similar to those lambs which were only subjected to handling. The use of local anaesthetic to castrate piglets was also shown to have a significant effect. Behavioural or action scoring is widely used in lameness assessment in horses. Regional analgesia of the limbs is used throughout equine clinical practice to locate the site of pain causing the lameness; numerous means of quantifying the lameness are used, from a score out of 10 to weight bearing as assessed by a force plate. More sophisticated gait evaluation is also used through computer analysis of videotapes of horses moving on a treadmill. However, the latter is used primarily for gait analysis rather than evaluation of lameness and analgesia.

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 & 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 (AVTRW Association of Veterinary Teachers and Research Workers, 1986; LASA, 1990; Flecknell, 1991; ILAR Institute of Laboratory Animal Resources, 1992; FELASA, 1994). Surprisingly, progress in validating this hypothesis has been remarkably slow. An early report (Leese, Husken, & Morton, 1988) indicated that the technique could be applied successfully, but the few subsequent published data are less encouraging. Particular problems noted were the considerable between observer variation and the poor predictive value of certain of the parameter scored (Beynen, et al. , 1988; Beynen, et al, 1987). The between observer variation is not unexpected, and parallels problems recognised in human pain scoring.

The most extensive, and best validated, studies in laboratory animals have been undertaken to investigate chronic pain, for example those by Colpaert et al (1980; 1982a; 1982b; 1987) and Colpaert (1987), using an adjuvant arthritis model in the rat.

Body weight, minute volume of respiration, mobility, vocalisations, specific behaviours and self-administration of analgesics were all considered as indices of pain. When discussing the results of all of these investigations, the authors concluded that all of the parameters responded to the same stimulus, and that the most reasonable explanation was that they were influenced by the presence of pain (Colpaert, 1987).

Motor behaviour changes have been suggested as indices of pain (Chudler & Dong, 1983; Wright, Marcella, & Woodson, 1985) and loss of appetite and reduction in body weight have been noted in rodents post-operatively (French et al, 1986 and 1988; Morton et al, 1985; Wright et al, 1985). Recently, 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 (Flecknell & Liles, 1991; 1992; Liles & Flecknell, 1993a; 1993b, 1994; Liles et al, 1997, Hayes and Flecknell, 1998, Flecknell et al, 1999). 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. As with other pain assessment techniques in animals, most of the studies described above assumed that if a change to a variable occurred after a procedure that would cause pain in man, then the change may be related to pain in the animal. If administration of an analgesic reverses the changes associated with the procedure, this supports the hypothesis that the changes were, at least in part, pain related. This is a somewhat circular argument, since it is simply stating that indices of pain are those indices that are normalised by administration of analgesic drugs. Although efficacy of these analgesics in reducing peripheral nociceptive input in animals is well established, (Crepax & Silvestrini, 1963; Taber, 1974; Albengres et al, 1988; Kistler, 1988), their effects on clinical pain are only validated in humans. Clearly it is also important to establish that the analgesic did not have non-specific effects in normal animals that would influence the variable studied. Unfortunately, this has rarely been done in companion animals, so that many of the pain scoring systems could have been influenced by the side-effects of the analgesics used. Similarly, almost no studies in companion animals have compared scores in animals which have undergone surgery with those that have only been anaesthetised (note, however, Firth and Haldane, 1999). The importance of controlling for these effects has been demonstrated in rats, when the effects of buprenorphine on behaviour in normal animals prevented accurate assessment of its effects following surgery (Roughan and Flecknell, 1997). Even more critically, many investigators have felt it was unethical to include a group of animals which underwent surgery, but did not receive an analgesic. The need for inclusion of a control group that undergoes surgery but receives no analgesic is clearly one that requires careful consideration. Many studies of pain in companion animals are undertaken in veterinary schools, where the standard practice for many years has been to assume that animals require pain relief following surgery, and to administer analgesics. Nevertheless, if the pain scoring systems used are believed to be accurate and reliable, then it is possible to devise a humane study which includes an untreated control group, but which incorporates intervention therapy if the pain score increases above a pre-defined threshold. It is also relevant to note that routine use of post-operative analgesia in both companion and laboratory animals is still far from widespread or uniform, and the information obtained from well controlled studies could be of considerable benefit to substantial numbers of animals. An alternative to use of a control group with intervention therapy would be to delay administration of the analgesic regimen

until after full recovery from anaesthesia, as has been done in some studies of post-operative analgesia in children (McIlvaine et al, 1988). 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 (eg 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 eg 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
- 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, empirical treatment of presumed painful conditions will continue, and it is not unreasonable to assume that analgesic therapies shown to be effective in man are likely to also be effective in animals. Although the assessment of clinical efficacy may not have been completed, studies of novel analgesic compounds and delivery systems in animals have established their safety and efficacy in analgesiometric tests. Analgesics can be broadly divided into two groups, the opioids or narcotic analgesics and the non-steroidal anti-inflammatory drugs (NSAIDs) 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 1-4.

## **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 pre-existing medical condition, 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**

One of the most important advances in the control of peri-operative pain has been the realisation that the timing of analgesic intervention may have a significant bearing on the intensity of post-operative pain. The concept was originally formulated early in the 20th century, by Crile (Crile, 1913), based on clinical observations. Crile suggested using regional blocks with local anaesthetics, in conjunction with general anaesthesia, to prevent postoperative pain in humans and the formation of painful scars caused by alterations in the central nervous system as a result of the noxious stimulation caused during surgery. Interest in this concept was revived when it was found that changes in the central processing of noxious stimuli occurred in response to peripheral injury (Coderre, 1993, Woolf, 1993). This change was suppressed to a greater extent by administration of opioids before, rather than after injury (Woolf, 1986, Dickenson, 1987, Chapman, 1993). These initial findings led to the development of the concept of "pre-emptive analgesia" - administration of analgesics before noxious stimulation begins, to prevent the adverse central nervous system (CNS) changes that this stimulation induces. To be most effective, pre-emptive analgesia must prevent the noxious stimuli from reaching the central nervous system. It should also aim to reduce or eliminate peripheral inflammation, which in itself increases input into the CNS, and so aggravates central hypersensitivity.

A positive effect of pre-emptive drug administration has been found experimentally (Woolf, 1986, Dickenson, 1987, Lascelles, 1995) and clinically in animals given opioids (Lascelles, 1997) and NSAIDs (Welsh, 1997; Lascelles, 1999). To gain maximum benefit, the matching of nociceptive input and analgesic medication is crucial to exploiting the clinical benefit of pre-emptive analgesia. In other words, the greater the surgical stimulus expected, the greater the degree of pre-emptive analgesia that must be administered. It is also important to appreciate that a single dose of analgesic, administered prior to surgery, will not usually be all the analgesia that will be required. Additional analgesic medication will still be needed in the post-operative period, but this pain will be more easily controlled because pre-emptive analgesia has been used. A further practical advantage of pre-emptive analgesia is that it will often reduce the dose of anaesthetic drugs required, and by integrating analgesic therapy into a balanced anaesthetic regimen, patient safety can be improved, in addition to providing more effective pain relief (see below).

In some circumstances, it may not be possible to administer analgesics pre-emptively, nevertheless, administering analgesics as soon as is practicable is of significant benefit. The longer pain is established, the greater will be the degree of central hypersensitivity, and the more difficult pain management becomes. Of particular interest in this respect is the effect of ketamine, as this drug has the potential to reverse central hypersensitivity because of its actions as an NMDA antagonist. Administration of ketamine at sub-anaesthetic doses (eg 0.1mg/kg in dogs and cats) may help provide analgesia in such cases, although no clinical trials have been carried out to confirm the practical significance of this effect.

## **"Multi-modal" Pain Therapy**

Clinical pain arises from a combination of central and peripheral hypersensitivity

involving a multiplicity of pathways, mechanisms and transmitter systems. So it is unlikely that a single class of analgesic will completely alleviate pain, irrespective of the dose used. In order to provide the most effective clinical pain relief, drugs of different classes will be required, 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 limit the nociceptive information entering the CNS as a result of the inflammation. By acting on different points of the pain pathways, the combination is more effective than either drug given alone. Adding a local anaesthetic to this regimen can provide additional analgesia by blocking specific nerve pathways, and so further improve the degree of pain control.

Using combinations of different classes of analgesics can also overcome some of the problems associated with differences in the speed of onset of action of the various agents. In a study comparing the degree of post-operative analgesia provided by pethidine and carprofen in dogs, animals which received pethidine had good analgesia immediately following recovery from anaesthesia, compared to animals which received carprofen (Lascelles et al, 1997). In contrast, dogs receiving carprofen had better analgesia later in the post-surgical period. Similar results were seen when comparing butorphanol with carprofen. Clearly, combining the two analgesics would produce a more effective regimen for controlling post-operative pain.

## **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 (eg ketamine and alpha 2 adrenoreceptor agonists such as medetomidine) and analgesics may be used as part of the analgesic regimen (eg 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 planning a peri-operative analgesic protocol.

## **Pain relief - problems**

A number of clinical problems arise when analgesics are administered to control post-operative pain. The most important problem is the short duration of action of most of the opioid (narcotic) analgesics. Maintenance of effective analgesia with, for example, pethidine, may require repeated administration every 1-3 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, rodents, rabbits and pigs that it has a duration of action of 6-12 hours (Cowan et al, 1977; Dum & Herz, 1981; Flecknell & Liles, 1990; Heel et al, 1979; Hermansen, 1986). In clinical use in a wide

range of animal species, it appears to provide effective pain relief for 6-12 hours. Its duration of action in the sheep appears to be considerably less, although still of longer duration than pethidine and morphine (Nolan, et al, 1987). An alternative approach is to adopt the well-established human clinical technique of administering analgesics as a continuous infusion. Infusions of analgesics have the advantage of maintaining effective plasma levels of the analgesic, so providing continuous pain relief. This is in contrast to intermittent injections, where pain may return before the next dose of analgesic is administered. This technique obviously poses some methodological difficulties in animals, but if an indwelling catheter and harness and swivel apparatus are available, then this can be arranged quite simply. In larger species (>3-4 kg body-weight), a light-weight infusion pump (Graseby Medical,) can be bandaged directly to the animal and continuous infusion made simply by means of a butterfly type needle anchored subcutaneously or intramuscularly. When analgesics are to be administered by continuous infusion, the infusion rate can be calculated from a knowledge of the pharmacokinetics of the analgesic to be used (Mather, 1983). If these data are not readily available, an approximation that appears successful in clinical use is as follows: calculate the total dose required over the period of infusion, reduce this by half and set the pump infusion rate accordingly; administer a single, normal dose of the drug as an initial loading dose and start the infusion. The rate can then be adjusted depending upon the animal's responses.

## **New routes of administration**

Attempts to provide both longer period of pain control, and more effective analgesia, have led to the use development of alternative methods of drug delivery. The majority of these techniques have been developed in man and some have been used successfully in companion animals.

## **Epidural and intrathecal opioids**

Epidural and intrathecal opioids have been shown to have a prolonged effect in man, and to provide effective analgesia (Glynn, 1987). In animals, clinical studies and experimental have indicated that the technique can be used in a number of species (Dodman et al, 1992; Popilskis, et al. , 1993; Pascoe, 1993; Pablo, 1993; Duke et al, 1993). Although used as a research tool in laboratory species (Yaksh, Al-Rodhan, & Mjanger, 1988), this route of administration has yet to be exploited as a means of controlling postoperative pain. The necessary techniques of epidural or intrathecal injection have been described in the rabbit (Kero et al, 1981; Hughes et al, 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 (eg Thurmon et al, 1996; Hall and Clarke, 1992)

## **Oral administration**

The need for repeated injections of analgesics is time consuming and may be distressing to the animal, particularly smaller specie which require firm physical restraint to enable an injection to be given safely and effectively. In addition, the need for repeated injections requires veterinary or other staff to attend the animal overnight. to circumvent this problem, the possibility of incorporating analgesics in food or water has been investigated (Kistler, 1988). Long-term analgesia can be

produced by this route, Kistler, 1988) reported that rats had demonstrable analgesia for a two week period when buprenorphine was administered continuously in the drinking water. Unfortunately, several practical problems limit the use of this technique. Some animals eat and drink relatively infrequently, or may only do so in the dark phase of their photo period. In addition, food and water intake may be depressed following surgery, and this, coupled with wide individual variation in consumption make 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. Rats receiving buprenorphine jelly had a significantly lower reduction in body weight, due to maintenance of a more normal pattern of food and water consumption.

Techniques for administration of food pellets at intervals to experimental animals are well-established, and it would be a relatively simple procedure to introduce an automated means of delivering pellets at appropriate time intervals. The technique could also be used with larger species, and need not be restricted to opioids, or indeed analgesics. Provided that the animal is eating or drinking, small quantities of highly palatable material could be provided at appropriate intervals. Simple timer devices to achieve this are already marketed for delayed feeding of pet dogs and cats.

As mentioned above the 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 (eg 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, 1997). We have frequently observed rats chewing the synthetic sheepskin bedding ("Vetbed" Alfred Cox) in the incubator used for recovery from anaesthesia, but this behaviour is short-lived. In studies carried out in our laboratory, no rats have developed signs of gastric distension, but there are

reports of gastric obstruction occurring after use of buprenorphine. It seems likely that this effect varies with the strain of rat, and the anesthetic 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. Pain relief in the immediate recovery period can be provided by including an analgesic drug in any pre-anaesthetic medication. Alternatively, 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 (Flecknell, Liles, & Wootton, 1989; Latasch, 1984; Robertson & Laing, 1980). The expertise of the surgeon can also greatly influence the degree of post-operative pain. Good surgical technique which minimizes tissue trauma and the 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 the techniques discussed earlier aimed at providing good post-operative care.

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