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Assessing pain in animals — putting research into practice

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Abstract

Our ability to assess pain in animals in clinical situations is slowly developing, but remains very limited. In order to develop appropriate pain scoring schemes, numerous practical problems need to be overcome. In addition, we need to appraise realistically our current poor state of knowledge. Development of new scoring systems must be coupled with the increased education and training of those responsible for pain management, so that both the assessment and the alleviation of pain are steadily improved.

Keywords: *analgesia, animal, animal welfare, pain, pain assessment, pain scoring*

Introduction

The last decade has seen growing concern over the issue of pain and distress in animals. This concern has been reflected in a steady increase in interest in pain assessment and pain management amongst veterinary surgeons and others. Despite this increased interest and concern, the management of animal pain remains poor. For example the use of post-operative pain relief in companion animals is low (Dohoo & Dohoo 1996; Capner *et al* 1999; Lascelles *et al* 1999; Raekallio *et al* 2003). Even if analgesic use were to increase, pain management is likely to remain poor because we still have virtually no practically applicable means for evaluating the degree of pain, and hence the effectiveness of our analgesic therapy, in any species. Without a method of assessing pain we cannot determine the efficacy of analgesic therapy in individual animals, nor determine when therapy can be discontinued.

In a recent editorial (Short 2003), the need to develop a number of aspects of pain management was highlighted (individual points edited for brevity):

• Medications — the need to develop more medications, formulations and treatment modalities.

• Pharmacokinetics — the need for more information on the pharmacokinetics of analgesics in animals of different species.

• Vital signs — the diagnosis of painful conditions and the effectiveness of treatment need to be correlated with pain scoring as a vital sign, coupled with scientific evidence of drug bioavailability.

• Knowledge — the biggest challenges ahead of us will be in the education of all those involved in managing animal pain.

• Client relations — an understanding of how veterinary surgeons discuss the various issues with their clients.

If the results of animal pain research are to influence clinical practice, we must raise awareness and improve the knowledge of veterinary clinicians and others involved in animal pain management through better education. It is also essential that research projects provide these people with the appropriate tools to assess animal pain. Without commitment and the expertise to assess pain, all of the remaining action points become irrelevant. It is therefore important to examine what pain assessment tools we have, and how many of these are both appropriately validated and suitable for general use.

Pain assessment in farm animals

Behavioural and endocrine indicators of pain in lambs, cattle and pigs have been established by a number of different research groups (Noonan *et al* 1994; Lester *et al* 1996; Mellor & Stafford 2000; Molony *et al* 2002). These have been developed largely to aid in the evaluation of the welfare benefits of modifying standard agricultural practices such as tail docking, castration and dehorning. It has been repeatedly demonstrated that the use of local anaesthetics, either alone or in conjunction with modifications to the techniques commonly used, can reduce pain-related behaviours in lambs and cattle. Regrettably, economic considerations have limited the widespread application of the results of these studies. Recently, the practical application of improved methods of docking and castration has been demonstrated (Kent *et al* in press), and pain scored in a 'field' situation. The improved techniques increased the time taken for castration and tail docking, and required the purchase of an additional piece of equipment. It seems likely that widespread application of the improved methodology will require that these economic issues be addressed.

Since additional interventions, such as the administration of additional analgesics, are rarely contemplated following

these husbandry procedures, there has been less of a need to develop a robust pain assessment system for general use on farms. It is worth noting, however, that in the study quoted above (Kent *et al* in press) shepherds were able to use Visual Analogue Scoring (VAS) to correctly identify lambs experiencing less pain as a result of improved techniques. In some circumstances, identification of pain would lead to a modification of clinical practice, for example after Caesarean section in cattle. Although a high percentage (68%) of specialist cattle veterinarians administer analgesics after Caesarean section, attempts to develop practical pain scoring schemes have not proven successful (Watts 2001). This is largely because of the very considerable difficulties entailed in developing such schemes, and this is discussed further below. Despite these difficulties, it is encouraging to note that several pharmaceutical companies are now actively marketing NSAIDs (non-steroidal anti-inflammatory drugs) for use in presumed painful conditions in farm animals.

Pain assessment in companion animals

Two well-documented schemes for pain assessment in dogs have been developed (Firth & Haldane 1999; Holton *et al* 2001). In addition, numerous studies using pain scoring systems based on Visual Analogue Scoring, Numerical Rating Systems, or Simple Descriptive Scores, or using a mixture of all three approaches have been published (Brodbelt *et al* 1997; Mathews *et al* 2001). The different approaches adopted in these different studies highlight many of the problems involved in developing pain assessment schemes (Holton *et al* 1998). In their original study, Firth and Haldane (1999) carried out detailed behavioural assessments of dogs, both before and after surgery, and identified behaviours that were probable indicators of pain. However, when these criteria were used to identify animals that should have been experiencing pain (because they had undergone surgery and had not received an analgesic), the confidence intervals on the measures were wide. In addition, since only animals undergoing a single type of surgical procedure (ovariohysterectomy) were included, the broader applicability of the scheme cannot be properly evaluated. A different approach was adopted by Holton *et al* (2001). This group sought to identify descriptors of pain by consulting with experienced small animal clinicians, and then used sophisticated analytical techniques to reduce these descriptors to a set of words or phrases. These descriptors were then developed into a multi-dimensional pain scale. Validation of this scheme, by using it to correctly identify animals that have received varying degrees of pain relief following surgery, has not yet been undertaken. Until this validation has been completed it is difficult to judge the reliability of the scoring system. It is hardly surprising that when the scheme is used by clinicians, whose opinion shaped its development, it successfully predicts patterns of analgesic use. What is required is a randomised, blinded, placebo-controlled trial. This, however, poses certain ethical and practical difficulties (see below). Despite these problems, this system has been developed further and also combined with the Firth and Haldane scheme to produce a scoring system for clinical use (Hellyer 2002).

Ethical and other problems with pain assessment schemes

Many other pain scoring schemes have been described, but virtually none of these has been properly validated. Indeed, the descriptions of the scales used in some studies are so brief that it is not possible to make a judgement as to how useful the scoring system would have been. In general, these schemes suffer from a number of problems:

(1) The assessment criteria used are frequently highly subjective.

(2) The study design does not include untreated (surgery and no analgesia) control groups.

(3) The study design does not include anaesthesia and analgesia (and no surgery) control groups.

Since many schemes include some behavioural assessment, and anaesthetics and analgesics (notably opioids) can markedly change behaviour in normal, pain-free animals, the lack of appropriate controls makes the results obtained highly questionable. However, inclusion of such control groups can cause significant ethical problems to those undertaking pain assessment studies. The majority of these studies are carried out in veterinary schools in which students are taught that animals experience pain and that analgesics should therefore be administered. Deliberately withholding analgesics in circumstances thought likely to result in pain may therefore be considered unacceptable. This problem is addressed in studies of pain in human subjects by implementing an intervention analgesia protocol, so that if the subject is assessed as experiencing pain above a certain level, they are removed from the study and given an analgesic. This assessment can be carried out by someone not directly involved in the study. This approach has been used successfully in a number of veterinary clinical studies (Lascelles *et al* 1995; Grisneaux *et al* 1999) and in laboratory animals (Roughan & Flecknell 2003).

Other problems remain, however. In addition to poor study design, few scales have demonstrated linearity — ie is a score of 4 twice as painful as a score of 2? Furthermore, few have addressed the problems of between-observer variation in applying the scoring system. However, it is encouraging that when placebo controls are included it is possible to demonstrate significant effects of analgesic administration (eg Lascelles *et al* 1997), suggesting that some elements of the scale used are indicators of pain. Considerable additional work is required before any of these schemes could be considered sufficiently reproducible or robust for use in veterinary clinical practice. The assessment schemes have also examined pain only in dogs and cats — pain in birds, rabbits, small mammals, reptiles, amphibians and fish, all of which may undergo surgery in veterinary practice, has received virtually no attention.

Pain assessment in laboratory animals

It might be thought that pain assessment in this group of animals would be the most highly developed, given the great public concern regarding their welfare. Although suggestions for assessing pain have been published (Flecknell

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1984), these were largely based on subjective clinical criteria that had not been subjected to any form of validation. A proposal to develop more robust scoring schemes was published by Morton and Griffiths (1985), but attempts to apply this were largely unsuccessful (Beynen *et al* 1987), primarily because the variables selected for inclusion were not fully identified and because the scales used were not sufficiently well characterised. The scheme has proven much more successful when applied as a means of developing more humane endpoints for experiments (Cussler *et al* 1999). These problems were identified by the original authors, but the indiscriminate application of the system seems to have led to a failure in identifying animals in pain, and to some research facilities abandoning its application. This is to be regretted since, when applied carefully, the scheme provides a structured method for assessing animals and can be a useful aid for developing endpoints in a range of different situations.

Other potential indicators of pain in laboratory animals have included general locomotor activity and changes in food consumption and body weight (Flecknell & Liles 1991; Liles & Flecknell 1993; Liles *et al* 1998). These latter measures are objective and have been used to assess analgesic drug efficacy. However, they are retrospective measures and so cannot be used to modify analgesic therapy for a particular animal. They can, however, be used as a simple measure of post-operative recovery, and as a means of adjusting future analgesic regimens for similar animals undergoing similar surgical procedures.

Other pain assessment systems have aimed at identifying acute and chronic pain states for research purposes (eg D'Amour & Smith 1941; Dubuisson & Dennis 1977; Gyires & Torma 1984), but these have limited application in assessing pain in other situations. A range of different techniques has been developed for assessing the likely efficacy of analgesics. In many instances, these involve the application of a brief noxious stimulus, followed by quantification of the animal's response. Administration of analgesics usually modifies this response, for example by prolonging the latency to withdraw a limb or tail from the noxious stimulus. In addition to their primary use as a means of screening for potential analgesics in drug discovery programs, the results of these tests have been used to estimate dose rates of analgesics for clinical use (Flecknell 1984). However, such extrapolations must be made with caution. For example, estimates of appropriate doses of buprenorphine based on tail flick tests resulted in a recommended dose of 0.5 mg kg^{-1} in rats (Flecknell 1984), which is 10 times higher than the dose shown to be effective using post-operative pain scoring systems (Liles & Flecknell 1993; Flecknell *et al* 1999). Since high doses of this agent can have undesirable side-effects, it is important that care is taken when making these extrapolations. Although results of these types of test may not predict clinical efficacy, they do illustrate the very wide variation in response that can be encountered between different strains of rodent (Morgan *et al* 1999). This reinforces the importance of developing pain scoring systems. If appropriate pain scoring schemes cannot be used, dose rates are probably best estimated from the results of tonic analgesiometric tests such as the late-phase formalin test or the writhing test (Roughan & Flecknell 2002).

Recently, we have developed a behaviour-based scheme for assessing pain in laboratory rats following abdominal surgery (Roughan & Flecknell 2001). During the initial development of the scheme, the behaviour of rats was evaluated following a mid-line laparotomy with appropriate untreated, and non-surgery analgesic-treated controls being included. An initial study using buprenorphine as the analgesic was inconclusive because of the marked effects of this opioid on normal behaviour (Roughan & Flecknell 2000). A subsequent study using carprofen and ketoprofen successfully identified a series of behaviours that differentiated rats that had received analgesics following surgery from those that had not. These studies required detailed analysis of considerable periods of video-taped behaviour, and filming at night under red light. Therefore, although the scoring criteria were suitable as a research tool, they did not provide a practically useful scoring system.

Following this study, the more general utility of the system was assessed in a different strain of rat undergoing surgery as part of an unrelated research project. In these studies, the animals were placed in an observation cage for a 10 min period and the frequency of pain-related behaviours was assessed. It proved possible to differentiate animals receiving analgesics from untreated controls, and to demonstrate a dose-related effect of the NSAID meloxicam (Roughan & Flecknell 2003). Re-analysis of all of the behaviours shown by these rats confirmed that the same behaviours as those seen in our previous investigations were the most useful for developing a clinically applicable pain scoring scheme. When experienced staff (animal technicians, research workers and veterinarians) viewed selected video recordings from these animals they were unable to correctly identify the treatment groups. However, after viewing a short recording illustrating the key pain-related behaviours, their ability to identify animals that had, or had not, received analgesics greatly improved (Roughan & Flecknell in press).

These studies suggested that key behaviours could be identified and used to score pain following one type of surgical procedure in rats. Most recently, we have used the scoring system to assess the relative efficacy of different analgesics and their duration of action. In addition, the scoring system has been applied to rats undergoing a different surgical procedure, bilateral adrenalectomy. These animals perform a very similar range of behaviours to animals undergoing laparotomy, but there are differences in the frequency of particular behaviours, with back-arching being more frequent after mid-line laparotomy and belly-pressing more frequent after bilateral adrenalectomy. This is similar to the results of behavioural studies of lambs undergoing different methods of castration and tail docking (Molony *et al* 2002), in that different types of abnormal behaviour are seen after the different procedures. What is uncertain is whether behavioural changes in rats after various surgical procedures will

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differ greatly in type, or whether they will be drawn from a common group of abnormal, pain-related behaviours.

A further problem that is becoming apparent is that all of the rats studied during the development of the pain scoring system were anaesthetised with isoflurane, a very short acting anaesthetic that results in rapid recovery of consciousness. When recovery is delayed, or is associated with prolonged sedation, animals may fail to express pain behaviour. At present it is not certain whether this is because the animals are not experiencing pain, or whether the heavy sedation prevents them from showing signs of pain. The scoring system may also be influenced by other factors, such as fear and apprehension, and unexpected variations in behaviour between different strains of animal may be encountered. Nevertheless, this approach offers a step forward in developing a practically useful scoring system for use after at least some types of surgery in rats. What is not yet known is whether similar systems can be developed for other laboratory species, or whether a similar approach can be used to develop means of identifying and quantifying other types of pain in animals, including chronic pain states.

Practical applications

Given the current poor state of our ability to assess pain, it is unsurprising that the practical application of any of these pain scoring schemes remains very limited. Considerably more research is needed to develop appropriate tools for assessing pain in many species, and it is essential that we evaluate current schemes critically. If we do not, and they are promoted widely and then prove to be unreliable, this will dissuade veterinary clinicians and others involved in pain management from applying assessment schemes. A second problem that is emerging is that applying scoring schemes in either veterinary clinical practices, research facilities or on farms, will take a significant amount of time. Taking the assessment scheme for rats as an example, at least 5–10 min per animal is required, and subsequent assessments, for example at 1–2 h intervals, should be made in order to monitor the animals adequately. If 20 or 30 animals are involved, this can easily develop into a full time role for a member of staff. It is important that such schemes are developed and promoted however, because if we do not have a clear means of identifying animal pain, analgesic use will continue to be restricted.

In farm animal practice there is little information concerning the level of analgesic use generally, and for specific husbandry procedures such as castration, the use of analgesics remains very low. In companion animal practice the level of analgesic use is thought to be growing, encouraged by the launch of a number of new analgesic agents. It is difficult to assess the overall level of analgesic use in laboratory species. Although a recent survey indicates that the provision of post-surgical pain relief may be widespread in the UK (Hawkins 2002), this survey was of a highly selected group of facilities and may not reflect practice elsewhere. Reviewing research publications involving surgery in rodents highlights some worrying trends — analgesic use is almost never mentioned in some journals, despite the papers describing invasive surgical procedures. In several recent publications, the authors stated that analgesics were not given because the animals showed no apparent signs of pain (Lawson *et al* 2001; Labat *et al* 2002; Grau & Steiniger 2003); this reinforces the need to provide simple methods of identifying pain.

Although one point emphasised at the outset of this paper was the need to educate veterinarians and others involved in pain management, perhaps the need to educate the general public is even greater. Many of the issues surrounding pain management have economic dimensions, and consumers can influence practices by the choices they make. This has been illustrated recently in Switzerland, where the introduction of anaesthesia for the castration of piglets has been successful on some farms. This has been linked with education of the public to accept a higher price for their food on the understanding that it has been produced at a lower cost to the animal (U Schatzman 2002, personal communication).

Conclusion

The recent increase in interest in animal pain and its prevention and alleviation is to be welcomed. We must appreciate, however, that we currently have a very limited ability to assess pain intensity accurately. This limits our ability to prevent and alleviate pain. We must strive to develop robust, practically useful assessment schemes for a wide range of different animal species. We must do this for different types of both acute and chronic pain. If we can make progress towards this goal we will be able to manage animal pain far more effectively than is possible at present.

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