MANAGEMENT OF CANCER PAIN

B. Duncan X. Lascelles,
BSc, BVSc, PhD, MRCVS, CertVA, DSAS(ST),
Diplomate European College of Veterinary Surgeons
Diplomate American College of Veterinary Surgeons

Assistant Professor of Small Animal Surgery
Comparative Pain Research Laboratory,
Department of Clinical Science, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606, USA

INTRODUCTION

There is a significant amount of interest in human medicine in cancer pain, both interest in the neurobiology of the pain, and interest in novel methods to alleviate cancer pain. However we know little about the relationship between pain and cancer in animals. In 1978, Yoxall stated that, “It is surprising, for instance, how much a dog's quality of life, observed by the owner, may be improved by the administration of a simple analgesic if the dog is suffering from a tumour, which although painless on palpation, may be causing considerable chronic pain.” Despite this statement and the fact that obvious pain associated with specific tumours such as osteosarcoma has been emphasized for a long time as a diagnostic criterion, there is a complete absence of controlled studies primarily investigating the potential occurrence of cancer pain in companion animals and a complete absence of studies primarily investigating the alleviation of pain in animals suffering from cancer. There is almost nothing written about cancer pain in animals. In one of the recent and most comprehensive books on pain management, only 13 of 177 pages are devoted specifically to chronic pain in animals. In one of the most recent and comprehensive books on small animal clinical oncology, only 13 of 683 pages are devoted to pain control in cancer patients.

It is estimated that cancer pain could be managed in up to 90% of human patients with currently available drugs and techniques, but that problems related to health care professionals, patients and health care systems lead to frequent under-treating of cancer pain. The same drugs and techniques recommended for use in humans can probably be used to good effect in animals. Barriers to effective pain control in animals probably include:

i. Lack of appreciation that many cancers are associated with significant pain
ii. Lack of knowledge of drugs, drug therapy and other pain relieving techniques
iii. Inability to assess pain in cancer patients
iv. Lack of communication with clients and lack of involvement of clients in the assessment and treatment phases
v. Under-use of nursing staff for assessment and re-evaluation of pain in cancer patients

HOW COMMON IS PAIN RELATED TO CANCER IN DOGS AND CATS?

The actual prevalence of cancer in the pet population is very difficult to estimate. One study that looked at the cause of death in 2000 dogs presented for post-mortem examination. It revealed that 45% of dogs living to 10 years or older died of cancer, and with no age adjustment, 23% of patients presented for necropsy died of cancer. In a recent survey, 2000 respondents stated that cancer was a leading cause of death in both dogs (47%) and cats (32%). Cancer must have a significant level of prevalence in the pet population.

Not all tumours will be painful, and the amount of pain is likely to vary considerably from one animal to another, even in those with similar tumour types. The author’s experience, and the experience of others would suggest that, conservatively, 30% of these are associated with some degree of pain (oral, bone, urogenital, ocular, nasal, liver, invasive, cutaneous, gastrointestinal). That this figure is conservative is suggested by looking at the figures from human medicine. In humans, pain is experienced by 20-50% of patients when the lesion is diagnosed, by nearly half of the patients in active treatment, and by up to 90% of patients with far advanced or terminal cancer, with an overall average of about 70% of patients with advanced cancer. In addition to the potential pain from the tumour, pain in cancer patients can also be due to the therapy (chemotherapy, radiation therapy, surgery [both perioperative and postoperative, and conditions such as phantom limb pain]) and non-cancer concurrent disease, most notably osteoarthritis.

THE IMPORTANCE OF ALLEVIATING PAIN ASSOCIATED WITH CANCER, AND THE RELATIONSHIP BETWEEN CANCER AND PAIN

The alleviation of pain is important from physiological and also from ethical standpoints. The role of the veterinarian is to alleviate suffering and maintain the welfare of the animals in his or her care. Pain is one aspect that compromises welfare. The majority of veterinarians probably agree that is ‘right’ to alleviate the pain associated with cancer, and most of the lack of treatment, or
undertreatment, probably stems from a lack of knowledge, lack of recognition of pain, and lack of re-evaluation of patients. It does not usually stem from a lack of concern.

Physiologically, pain can induce a stress response, with elevations in ‘stress hormones’ (aldosterone, angiotensin II, antidiuretic hormone, adrenocorticotropic hormone, catecholamines, cortisol and rennin) and decreases in other hormones (insulin and testosterone). These changes result in a catabolic state, with muscle protein catabolism. A stress response can result in decreased healing, and can adversely affect the cardiopulmonary system and gastro-intestinal system. Such systems are stressed already by the presence of cancer.

Of interest is the recent finding that the provision of analgesics significantly reduces the tumour-promoting effects of undergoing and recovering from surgery. Undergoing surgery is well known to result in the suppression of several immune functions including natural killer (NK) cell activity in both animals and humans probably as a result of released hormones such as catecholamines and prostaglandins. This suppression of NK cell activity can enhance metastasis. The reduction in tumour promoting effects of surgery by analgesics seems to be due to the alleviation of pain-induced reduced NK cell function, but it is also likely that hitherto unrecognised factors other than immune cells probably also play a role. So the provision of adequate perioperative pain management in oncological surgery may be protective against metastatic sequelae in clinical patients. It may also be that the treatment of the chronic pain often associated with the cancer itself, and maybe also of non-cancer painful conditions such as osteoarthritis, may be somewhat protective against metastasis, and possibly the local extension of cancer. This is, as yet, unproven, but an interesting hypothesis.

ASSESSMENT OF CANCER PAIN AND WELFARE

It is likely that the tolerance of pain by an individual animal varies greatly from individual to individual, as it does in humans. Coupled with dogs’, and particularly cats’, innate ability to mask significant disease, and probably pain, this makes it very difficult to assess pain. Unfortunately, no work has been carried out on the assessment of cancer pain in cats or dogs. The mainstay of pain assessment in cats and dogs suffering from cancer is likely to be behaviour.

To be able to assess pain, the veterinarian needs to have a basic understanding of normal behaviour in that species. Ideally, the veterinarian should have knowledge of the individual animal’s normal behaviour. This is not possible in most cases, and so the best people to assess the animal’s behaviour are the owners. The veterinarian must work closely with the owner to both assess the level of pain present at the initial evaluation, and during the re-evaluations that must take place throughout treatment.

Particularly when dealing with the treatment of cancer, it must be remembered that all aspects of welfare should be evaluated. Pain is one aspect of welfare. A logical and comprehensive framework for the analysis of welfare of any animal is summarized by the five freedoms, originally proposed for use in farm animals, and more recently proposed for use in small animals; freedom from hunger and thirst; freedom from physical and thermal discomfort; freedom from pain, injury and disease; freedom to express normal behavior; freedom from fear and distress. The alleviation of pain is an important aspect of this, but should not be performed while other aspects are ignored, nor should the alleviation of pain result in compromises in other aspects of welfare.

PRINCIPLES OF ALLEVIATION OF CANCER PAIN

The use of drugs is the mainstay of cancer pain management, although adjunctive therapies are being recognised as increasingly important. The World Health Organisation has outlined a general approach to the management of cancer pain and it is based on the use of the following ‘groups’ of analgesics:

a. non-opioid analgesics (e.g non-steroidal anti-inflammatory drugs, acetaminophen)
b. weak opioid drugs (e.g. codeine)
c. strong opioid drugs (e.g. morphine)
d. adjuvant drugs (e.g. corticosteroids, tri-cyclic antidepressants, anticonvulsants, NMDA antagonists)

This ‘analgesic ladder’ was developed based on the premise that health care professionals should learn how to use a few drugs well. It is based on three stepped levels of treatment intensity. Some types of pain will respond to non-opioid therapy alone. Pain of a greater intensity can be combated with the combination of a non-opioid and a ‘weak’ opioid. More severe pain requires the addition of a higher dose of opioid, and the use of a ‘strong’ opioid that is titrated to the pain present. At any of these three levels, adjunctive analgesics can be used to augment analgesia. This approach is a sound one where the pain is initially at a relatively low level, and gradually becomes more severe.

There are two problems with the use of the WHO analgesic ladder in veterinary medicine. The first is that there is very little information in human medicine on which drugs are most effective for which particular types of cancer pain (see below), and virtually no information in veterinary medicine. It may well be that ‘4th tier’ drugs might be most effective for that particular condition, and best used up front.

The second problem is that such an approach is that it is not so suited to patients that already present in significant to severe pain. Many veterinary cancer patients present at such a stage. Once pain has been present for a period of time, changes have taken
place in the central nervous system that alter the way pain signals are processed. This alteration in processing (central sensitization) makes analgesics less effective, and requires that multiple classes of analgesics be used, concurrently, to minimise the pain. Once the pain is minimised, and central changes are partially reversed, the amounts of drugs being administered, and the numbers of classes of analgesic drugs being used, can be decreased. This approach is termed (by this author) the ‘analgesic reverse pyramid’ approach. It is currently unknown which of these two approaches is most appropriate, and indeed, one approach may be best at one disease stage, and the other later on.

Although drug therapy has traditionally been the mainstay of analgesic treatment of cancer patients in human medicine, and is likely to be so in veterinary medicine, the authors believe that non-drug therapies should be used whenever possible, in conjunction with appropriate drug therapy. There has been no assessment of non-drug analgesic therapies for cancer pain, but therapies such as acupuncture, nutraceuticals, neuroablative techniques, and radiation therapy all seem to be effective in certain circumstances. Palliative radiation therapy is playing a larger role in veterinary oncology as owners are seeking to make their pets more comfortable even if a long-term control is not possible. Keys to successful radiation including establishing goals of palliation, minimizing treatment related morbidity and hospitalization, making sure that radiation has a realistic expectation of helping patient. Too often patients are either treated palliatively when curative intent is more appropriate or treated when there is little expectation of improvement of quality of life. Careful consultation with the owner is critical to a successful outcome in palliative care. Most palliative protocols use lower total doses and a higher dose per fraction to accomplish the goals listed above. Owners must understand that this approach means not only that tumor control may be short term compared to definitive therapy, but also the risk for late effects are increased in the event the patient lives longer than expected. Palliative radiation has been used in many clinical settings in veterinary medicine, especially in the management of appendicular osteosarcoma, metastatic bone lesions and localized refractory lymphoma. Any tumor which is causing clinical signs or obstruction of organs may benefit from palliative radiation therapy. Again, the aims of therapy are to improve quality of life rather than prolonging survival times. As such, patients may not live longer, but will hopefully improvement in pain control during this phase of the disease process.

**TOWARDS A MECHANISTIC UNDERSTANDING OF CANCER PAIN**

Over the last few years, it has become evident that the pain transmission system is plastic, that is, it alters in response to inputs. It is also becoming understood that this plasticity results in a unique neurobiological signature within the peripheral and central nervous system for each painful disease. Reading and understanding the individual neurobiological signatures for different disease processes should allow novel, targeted and more effective treatments to be established. This approach should also allow for a more informed choice to be made regarding which of the currently available drugs might be most effective.

It may surprise readers that only in the last few years has the first relevant model of cancer pain has been established in rats – an osteosarcoma model. Prior to this, evaluation of mechanisms and treatments were undertaken in various chronic pain models such as sciatic nerve ligation, or injection of chronic irritants – models that did not involve cancer. The establishment of these more recent models, such as the osteosarcoma pain model, have shown that the neurobiological signature of pain in clinically relevant models is very different from that in the older models of chronic pain. The new approach of using clinically relevant models has allowed targeted pain treatments to be developed, for example, the use of osteoprotegerin for bone cancer pain. Such models will also allow for the screening of the potential efficacy of other novel treatments such as neuroablative techniques.

**REFERENCES**

The World Health Organization is developing new guidelines for the clinical management of cancer pain in adults. The production of these guidelines will be led by WHO’s Department for the Management of Noncommunicable Diseases, Disability, Injury and Violence Prevention (NVI). Previous WHO guidelines on this topic include the 1996 document ‘Cancer Pain Relief, 2nd Edition, with a guide to opiate availability’. In light of new evidence and strong mandates from Member States, new guidelines are needed. More recently, WHO has developed Guidelines on the pharmacological treatment of persisting pai...