



Molly Varga BVetMed DZooMed MRCVS

Molly Varga qualified from the RVC in 1992 and, after spending time working in Canada, returned to the UK where she has worked both in London and the North West. She holds the RCVS Diploma in Zoo and Wildlife Medicine and is a recognised specialist in this field.

Analgesia and pain management in rabbits

Molly Varga BVetMed DZooMed MRCVS

Rutland House Veterinary Hospital, St Helens, Merseyside WA9 4HU, UK and Manor Vets Edgbaston, Birmingham B17 8DL, UK

ABSTRACT: Rabbits are increasingly popular as household pets, and owners expect a high standard of care for them, in line with their expectation of our level of care for dogs and cats. This article considers the recognition and treatment of distress and pain in this species.

Introduction

Rabbits are popular pets, and are increasingly thought of as family members (in the same way as cats and dogs) rather than simply as a child's pet. One consequence of this is that owners are seeking more frequent veterinary care for these animals and are equally expecting the standard of care to match that of dog and cat medicine.

Rabbits pose several challenges both as pets and patients related to the fact that they, perhaps more than any other commonly treated species, are a prey animal. This means they have behaviour patterns that make it difficult for owners to recognise signs of distress in the home environment until matters have progressed so far that the animal doesn't care if its vulnerability is recognised. In the veterinary clinic environment it also means that recognition of pain and discomfort presents far more challenges.

In terms of treating these animals once pain is recognised, its causes and sequelae both need to be considered: rabbits are often more compromised than other, more familiar, species, meaning that the adverse effects of any drug administered may be magnified. RVNs are in an ideal position to be able to assess both, pain levels and the success of treatments in these patients.

Normal rabbit behaviour

Despite having been domesticated for around 500 years, the behaviour of so-called 'domestic' rabbits is little different from that of their wild counterparts (McBride, 2000). They are a prey species whose normal behaviour is to be active

between dusk and dawn, using these hours to feed, interact socially and mate, and the daytime is used to sleep, safe from predators in underground burrows. Rabbits are a social species and live in groups of 2–8 adults with associated juveniles; each group has a defined hierarchy and territory.

Because of the risk of predation, rabbits are constantly aware of their surroundings (they have almost 360° vision). They will, in the first instance, attempt to flee from danger. Another strategy often employed is hiding/becoming silent and still until the threat has passed. Any individual that can't display these behaviours is at increased risk of being predated, so it is safer to mask illness than show weakness.

Recognising pain

Recognising when a rabbit is in pain can be difficult because they are programmed to hide vulnerability. Unless there is significant acute pain, rabbits do not vocalise, although in some cases they will grind their teeth when they are uncomfortable. This can be hard to differentiate from the quiet grinding that happens when rabbits are content. While some owners are very attuned to their rabbits and may recognise the difference straight away, vocalisation is not a sensitive method of recognising pain in this species.

So how can we tune in to signs of their pain? If a rabbit has a painful condition, or has had a procedure that would be deemed to be painful or uncomfortable in another species, then it should be assumed, even in the absence of behavioural signs, that the rabbit is in pain. This is called 'inferred pain'. Despite pain being present, the

animal is exhibiting normal behaviour to avoid predation.

In other species, pain can be suspected when some normal behaviours, such as grooming or eating, are absent. To an extent this can be true in rabbits; however many rabbits are kept as part of a bonded pair, and, initially at least, it may be difficult to tell if one of the rabbits isn't eating. In addition, the companion will often perform some grooming on its mate, meaning that subtle signs can be missed. These signs may be easier to recognise in rabbits kept alone, however the stress of separating a bonded pair is significant and may not be outweighed by the advantage of being able to observe a rabbit alone.

Looking at mobility and alertness toward surroundings (particularly when the animal doesn't realise it is being watched) can be more informative. Rabbits that are in pain will reduce their mobility unless there is a perceived threat, and will often, by their body position, indicate the painful area. A rabbit that is in pain will also appear less aware of its surroundings as long as it does not realise it is being watched, however, should it become aware of being observed it will often normalise its behaviour. Understanding normal behaviour and an appreciation that perhaps more detailed monitoring is required in our rabbit patients is the key to prompt recognition of pain in this species. Keating, Thomas, Flecknell, and Leach (2012) have devised a useful pain-scoring system (Box 1 and Figures 1–7). The five facial action units should only be used on rabbits that are awake and until further

validation is undertaken they should not be used as the sole means of assessment of pain.

Physiological parameters that can support the diagnosis of pain in these patients include:

- fluctuations in body temperature
- elevated respiratory rate
- elevated heart rate
- elevated blood pressure

Box 1. Pain scoring (from Keating et al., 2012)

- Using the five facial action units and scoring these from 0 (not present) to 2 (obviously present)
- **Orbital tightening:** A normal rabbit's eyes will be wide open and the rabbit will be aware of and interested in its environment. A rabbit that is in pain will often partially or fully close its eyes and in cases of severe pain the eyeballs appear to be withdrawn into the head (Figure 1).
- **Cheek flattening:** a normal rabbit's cheeks will be relaxed and the whiskers will protrude giving information about the environment. A rabbit that is in pain will suck in its cheeks making the whiskers lie flat across the face, and giving the face an angular, pinched appearance (Figure 2).

- **Nose shape:** a normal rabbit's nose is constantly twitching and the nostril slits (nares) are around 30° from the horizontal. When a rabbit is in pain, the nostril slits are drawn upwards, bringing them closer to a vertical position (Figures 3 and 4).

- **Whisker position:** a normal rabbit's whiskers will stick outwards from the face, however these will be pulled in and flattened towards the cheek when a rabbit is in pain (Figures 5 and 6).

- **Ear position:** except in the case of lops, a rabbit's ears are usually perpendicular to the head. Where a rabbit is in pain, the ears are pulled back to become flattened towards the back and the sides of the body (Figure 7).

Physiology of pain

The pathophysiology of pain in rabbits is similar to that of other mammals. When damage to tissue occurs, the damaged cells release chemicals that stimulate nerve endings (nociceptive receptors or nociceptors). If stimulated strongly enough, the nerve endings send an action potential through the nerve to the spinal cord and brain resulting in the sensation of pain. This allows the animal to become aware that tissue damage is occurring, facilitating evasive action if appropriate. Because pain involves cognition and emotion as well as behaviour, there is an integrated

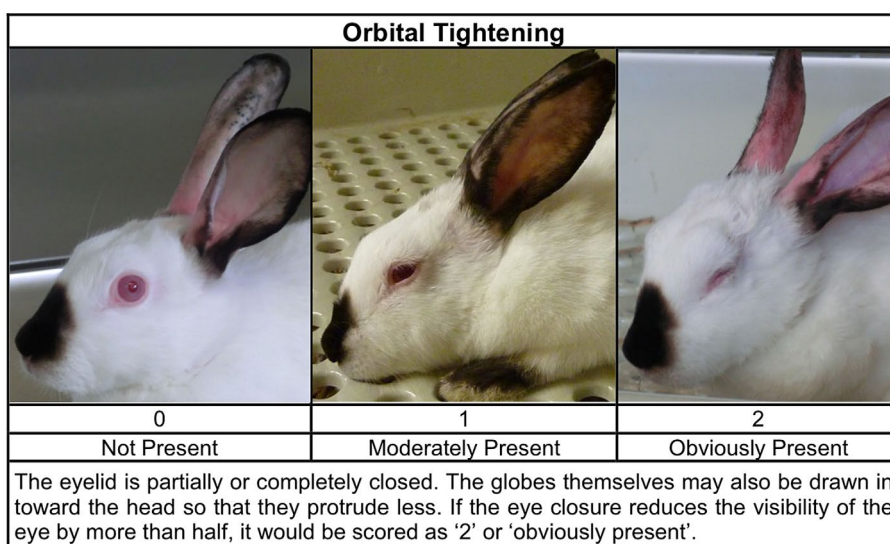


Figure 1. Examples of orbital tightening

Credit: University of Newcastle Pain and Animal Welfare Sciences Group



Figure 2. Example cheek flattening

This picture shows a rabbit with an atypical myxomatosis lesion on its nose: the cheeks are flattened and the whiskers are down



▲ **Figure 3.** Examples of nasal slant
Credit: University of Newcastle Pain and Animal Welfare Sciences Group

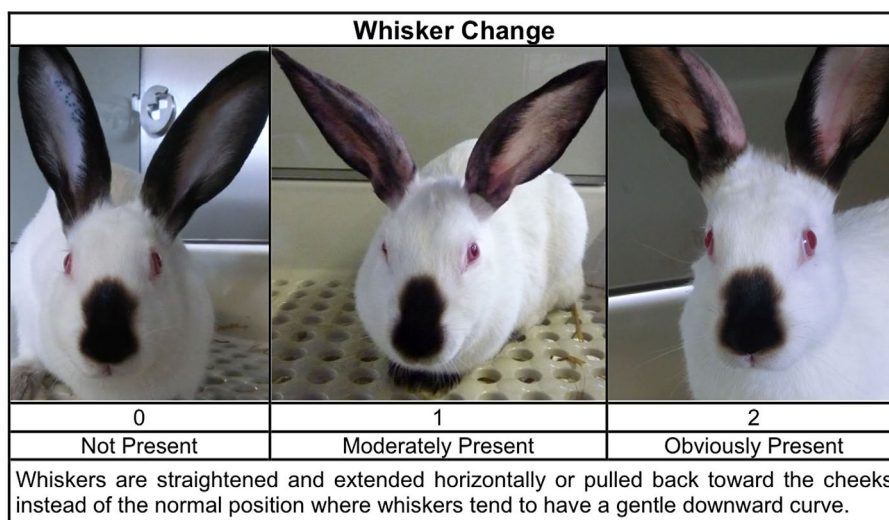


▲ **Figure 4.** Examples of nasal slant

response to a painful stimulus from many parts of the brain. Some terms used in the discussion of pain are shown in **Box 2**.

▲ **Box 2.** Definitions

- **Analgesia:** absence of pain in response to a stimulus that would normally be painful
- **Hyperalgesia:** an increased response to a stimulus which is normally painful
- **Nociceptor:** a receptor preferentially sensitive to a noxious



▲ **Figure 5.** Examples of whisker position
Credit: University of Newcastle Pain and Animal Welfare Sciences Group



▲ **Figure 6.** Examples of whisker position

(painful) stimulus or to a stimulus which would become noxious if prolonged

- **Noxious stimulus:** noxious stimulus is one which is damaging to normal tissues
- **Pain threshold:** the least experience of pain which a subject can recognise
- **Pain tolerance:** the greatest experience of pain a subject can tolerate
- **Neurogenic pain:** pain initiated or caused by a primary lesion or dysfunction or temporary perturbation in the peripheral nervous system
- **Neuropathic pain:** pain initiated or caused by a primary lesion or dysfunction in the nervous system
- **Wind-up pain:** an increase in perceived pain intensity over time, when a given stimulus is repeatedly applied; lasts for a short period of time, however can lead to 'long-term potentiation' and become part of a chronic pain state

Descending control pathways

In some circumstances, such as when an animal's safety is in jeopardy, a lack of pain awareness and response is beneficial (a speedy flight response despite an injured leg, for example). This can be clearly recognised in rabbits. The descending pathways (termed *descending control pathways*) that inhibit pain perception are called *antinociceptive*. Stimulation of these sites can result in inhibition of pain-recognising neuronal activity. They also inhibit those behaviours and reflexes normally induced by a noxious stimulus. Endogenous analgesia (*antinociception*) is closely tied to the behavioural and emotional state of the animal and to the autonomic system. Thus, the experience of pain is the outcome of many complex processes.

Stress

Pain is a stressor and causes an endocrine stress response with release of cortisol, catecholamines and other stress hormones. Release of these hormones causes a host of physiologic and metabolic changes, including tachycardia, hypertension, immune system alterations, hyperglycaemia, lipolysis and a negative nitrogen balance (Loeser, Butler, Chapman, & Turk, 2001). The consequences of these changes can be severe, (**Box 3**). Modern pain treatment in human patients recognises the significant benefit of analgesia with respect to the reduction of the stress response and improved recovery of patients.

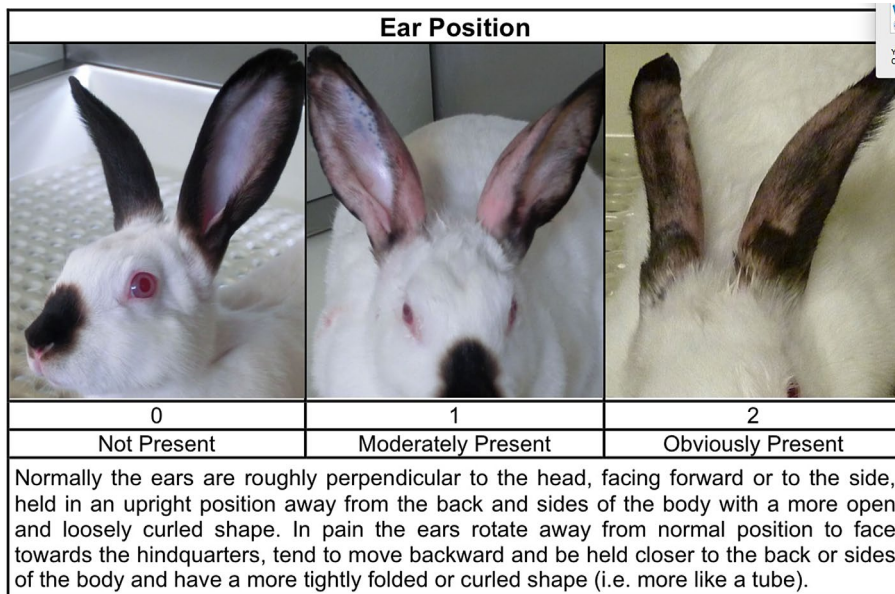


Figure 7. Examples of ear position
Credit: University of Newcastle Pain and Animal Welfare Sciences Group

Box 3. The consequences of stress in rabbits

- heart failure and death
- cardiomyopathy
- reduced gastrointestinal mobility leading to gut stasis
- an increase in gastric acidity potentially leading to gastric ulceration
- reduced renal perfusion and filtration leading to reduced urine production
- immunosuppression
- anorexia which can result in hepatic lipidosis
- alterations to carbohydrate metabolism leading to elevated blood glucose levels

Recognising and managing concurrent disease factors

Many rabbits that are experiencing pain have other significant clinical conditions concurrently that affect the safety of some of the analgesic medications that may be administered. The biggest impact on medication safety is dehydration.

Dehydration

Dehydration can be recognised in a similar way to other species with some cautions. Rabbit skin is normally very loose, so a noticeable skin tent only occurs with severe dehydration (10–15%). Mucous membrane tackiness is a more

reliable indicator (as long as the rabbit has not just been drinking). Sunken eyes and prolonged capillary refill time may also be noticed. It is also worth mentioning that rabbits can experience severe dehydration due to fluid shifts into the gut without showing a change in weight, so reliance on regular weighing can be falsely reassuring.

Any rabbit with fluid deficits should at least be in the process of having these corrected before the administration of any drug that can adversely affect renal function.

Anorexia

Anorexia is another common sequel of pain and this can also affect the oral administration of medications. A normal rabbit should really never have an empty stomach, and with a post-prandial pH of 1–2 in addition to the effects of stress; gastric ulceration is a very real concern. Oral non-steroidal anti-inflammatory drugs (NSAIDs) in particular should be administered with caution until feeding is re-established, with support feeds being given as necessary. It's worth remembering however that good pain relief is often instrumental in re-establishing feeding.

Analgesic drugs

Non-steroidal anti-inflammatory drugs

Various NSAIDs can be used in rabbits. By far the commonest is meloxicam because of its liquid formulation. This allows accurate calculation and administration of the dose, with the added benefit that most rabbits enjoy the taste. Meloxicam is a COX-2 selective medication and has a low incidence

of side effects, although the possibility is increased at higher doses. Because meloxicam and its metabolites are excreted via the liver in the faeces, there is the possibility of re-ingestion. Some rabbits given meloxicam appear to have altered taste perception and change their dietary preferences, and some may reduce or stop the intake of caecotrophs.

Another advantage of meloxicam is the fact that there is a fair amount of research available to support the doses and dosing intervals used in rabbits (Carpenter, Pollock, Koch, & Hunter, 2009; Cooper, Metcalf-Pate, Barat, Cook, & Scorpio, 2009; Delk, Carpenter, KuKanich, Nietfeld, & Kohles, 2014; Fredholm, Carpenter, KuKanich, & Kohles, 2013). Rabbits require a much higher dose than a dog of the same weight (approximately eight times the dose) and require this more often (twice daily rather than once daily dosing).

Other NSAIDs that can be used include carprofen and ketoprofen. As both of these medications are only available as tablets in the oral formulation, dosing can be problematic and is certainly less accurate in smaller individuals. Equally there is less validated research on the use of these drugs in rabbits.

Opiates

Opiates or narcotic analgesics reduce pain perception by interacting with opioid receptors on cells. They are used in episodes of acute severe pain (e.g. surgery or trauma) and in the management of chronic intractable pain (severe osteoarthritis, for example).

Opiates can be grouped into three categories, according to their mode of action:

- Pure agonists (including morphine, methadone and fentanyl): provide excellent analgesia but tend to be fairly short acting, meaning either constant rate infusion (requiring accurate fluid delivery to small patients) or repeat dosing (and potentially increased stress) is required.
- Mixed agonists/antagonists (such as butorphanol): the advantage of mixed agonist/antagonist preparations is that while providing analgesia they also partially reverse the sedative qualities of pure agonists. Butorphanol exhibits a ceiling effect (that is a dose above which there is no additional analgesic effect noted, only a magnification of the side effects).
- Partial agonists (buprenorphine for example): buprenorphine has a relatively slow onset of action. It does however have a good safety profile in rabbits.

Side effects of opiate drugs are dose dependent and can include sedation, respiratory depression, reduced gut motility and bradycardia.

Miscellaneous analgesics

Alpha-2 agonists: ultra-low doses of alpha-2 agonists (medetomidine, dexmedetomidine) can be used together with other drugs (i.e. opioids or a tranquilliser) to result in analgesia that is combined with muscle relaxation and a degree of sedation. At the ultra-low doses, alpha-2 agonists display minimal effects on monitoring parameters such as heart rate, respiratory rate and blood pressure.

Gabapentin is an anticonvulsant medication that can modify the perception of neurogenic pain. It may result in ataxia and sedation, which are dose dependent, and this medication should not be stopped abruptly because this has led to seizure activity in other species.

Tramadol is a synthetic, opioid-like drug. Evidence relating to its use in rabbits is sparse, however it does appear to provide good analgesia and is very suitable for long term use, and indeed in cases where long term NSAIDs are contraindicated it can be used as a replacement for these (Souza, Greenacre, & Cox, 2008).

Ketamine at low doses (often within a constant rate infusion, with an opioid) can be used in pain management of patients in hospital. It acts on NMDA receptors as an antagonist and prevents or reduces wind-up pain.

Paracetamol exhibits mild analgesic effects the mode of action of which is poorly understood. It may be used in combination with other analgesics, but its potential for causing hepatic, renal and gastrointestinal side effects can reduce its usefulness in rabbits.

Local anaesthetics

The use of local anaesthesia, particularly in reference to planned surgical intervention, is well recognised. Splash blocks, ring blocks, topical applications and local infiltration can all be used. Depending on the drug, the effects can last from 30 minutes to several hours. In combination with other pain-relief modalities, local anaesthesia can make a significant difference to presence or absence of wind-up pain, and reduce interference with surgical wounds.

Other modalities

Drugs are not the only option to consider when planning and evaluating pain control in rabbit patients

Acupuncture

Acupuncture is well tolerated in rabbits, although it does depend on the individual animal. The neuromodulation induced by direct nerve stimulation alters the transmission of pain signals to the spinal cord and brain. Acupuncture can significantly improve pain control in chronic conditions such as osteoarthritis, especially when applied regularly.

Transcutaneous electrical nerve stimulation (TENS)

TENS provides pain relief using a mild electrical current, which reduces the pain signals going to the spinal cord and brain. It may also stimulate endorphin production. Rabbits appear to tolerate TENS very well.

Laser therapy

Laser therapy works by modulating inflammatory mediators leading to anti-inflammatory and analgesic effects. Rather than direct nerve stimulation or the use of electrical current, therapeutic laser works using pulses of light. There are apparently no side effects, and the therapy is very useful for chronic conditions such as osteoarthritis. Again laser therapy is very well tolerated in rabbits.

Nursing care plans

Increasingly, nursing staff are being encouraged to develop personalised nursing care plans for their patients, developing the provision of holistic nursing care (Nelson & Welsh, 2015). Whilst nurses are not allowed by law to make a clinical diagnosis, the nursing care plan rests on the formulation of a nursing diagnosis allowing the effectiveness of any interventions (for example pain relief) to be scored, providing invaluable feedback to the veterinary surgeon. Nursing staff are in the best position to determine the effectiveness of a pain relief plan.

Multimodal analgesia and pre-emptive analgesia

Multi-modal analgesia is the use of several drugs or therapies together in order to achieve the best effect for the patient. A good example of this would be using an NSAID, an opiate and a local anaesthetic block to provide pain relief after surgery. Pre-emptive analgesia is the provision of pain relief before a planned intervention that is likely to be painful, for example using an opiate drug in a premedication protocol.

When considering rabbit patients, both pre-emptive and multimodal approaches

make a lot of sense (Barter, 2011; Weaver, Blaze, Linder, Andrutis, & Karas, 2010). Because stress and pain can lead to significant complications in these patients, making certain that pain is accounted for, as well as reducing the environmental stress can significantly improve clinical outcomes.

Conclusion

Recognition of pain and implementation of appropriate pain relief can significantly improve both the welfare and the clinical outcome of our rabbit patients. Nursing staff play a key role in determining the effectiveness of the pain relief provided and in feeding back to the veterinary surgeon when signs of pain are recognised despite treatment, allowing rapid and appropriate intervention.

Acknowledgements

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