A considered approach to opioid use

Though opioids still have a place in veterinary analgesia, there is a growing body of evidence which suggests that they should not be considered the gold standard for perioperative analgesia.

Opioids have been the cornerstone of the development of modern veterinary anaesthesia and analgesia. Gone are the times when pain served the purpose of “protecting the surgical site” from excessive use. Luckily, we have now moved away from the “no pain, no gain” approach to pre-operative analgesia, at least in small animals.

Opioids have been a lifeline for veterinary anaesthetists when administering pre-anaesthetic medication, inducing anaesthesia and providing post-operative analgesia, even in the sickest animals. I cannot think of many conditions in which animals are deemed not to be sufficiently fit to receive an opioid analgesic. Thanks to opioids, we can now perform very invasive procedures and can relieve post-operative pain until animals can be discharged and sent home. As veterinary anaesthetists, we are particularly lucky because side effects of opioids in animals are generally very mild compared to people. It is objectively difficult to overdose a dog with an opioid, and in the past 15 to 20 years, analgesic protocols for species more sensitive to the behavioural side effects of opioids, for example cats and horses, have been developed successfully.

Opioids are such a relevant part of our daily anaesthetic routine that we now have dedicated veterinary products covering most of our needs, from a short-acting full agonist, to longer-acting full and partial agonists. It is unquestionable that the overall effect of increased opioid use on quality of perioperative care has been positive. The big question is: at what price?

Side effects of opioids

Less obvious, but more insidious, side effects of opioids have been investigated in people and in experimental animals suggesting that, under certain conditions, they may induce hyperalgesia (increased sensitivity to pain) and even contribute to metastatic spread of cancer.

While the effects of opioids on immunity have been investigated in people, little is known about the effect of perioperative opioid use on metastatic rate after cancer surgery in animals. Opioid-based perioperative analgesia increases the risk of cancer recurrence and metastasis in breast and prostate cancer, compared to perioperative analgesia protocols based on locoregional anaesthesia.

The exact mechanisms underlying the pro-metastatic effects of opioids in certain types of cancer are not fully understood. However, immune cells, endothelial cells and tumour cells express opioid receptors, and greater expression of the mu opioid receptor in some tumours has been linked to poorer outcomes.

Administration of physiological doses of morphine triggers intracellular events that promote angiogenesis, mitosis and therefore tumour growth, at the same time decreasing the activity of natural killer cells. While knowledge of the clinical relevance of this is currently limited in animals, its importance is such in people that “opioid free” anaesthetic techniques are becoming more and more common, and new non-opioid analgesic agents are currently being investigated.

Opioid induced hyperalgesia (OIH) has been long recognised, yet poorly characterised clinically, and has baffled medics and scientists; how could a drug that reduces pain increase sensitivity to pain? Recognition of OIH in a clinical setting is not unequivocal, as persistent pain may simply be the effect of inadequate analgesia, rather than the manifestation of a more elaborate biological phenomenon.

OIH is a distinct entity from tolerance, although the two share some common molecular mechanisms. Tolerance manifests itself as decreased sensitivity to analgesic effects of opioids, usually due to long-term treatment, and increasing the administered dose restores analgesia.

OIH, on the other hand, is characterised by pain sensitization and cannot be reversed by increasing opioid dose. Experimental animal models have demonstrated increased sensitivity to pain after administration of various opioids and using different routes. Acute administration of high doses of opioids to rodents results in a biphasic response,