Making Education Easy

Issue 9 – 2019

In this issue:

Abbreviations used in this issue

ECC = Emergency and Critical Care
CSF = cerebrospinal fluid
FIP = feline infectious peritonitis
OR = odds ratio
γIFN = interferon gamma

Welcome to Issue 9 of Companion Animal Research Review.

Just in time for spring, we have bloomed this edition for you, and as ever, hope you find it as uplifting as the sight of newborn lambs. Whilst it is not a replacement for your normal bedtime textbook reading, it may deserve its own secure, if humble place in the pantheon of educational options available to lift you from the burden of an otherwise stagnant professional existence. Or at least, it may serve as a mild diversion. In this edition we range from the benign of what predicts owner compliance, through the bizarre of itraconazole as a treatment for feline infectious peritonitis, to what might be the ridiculous of whether adolescent girls love puppies more than boys do. Please do let us know when, of if ever you find these useful, and don't be afraid to voice your suggestions for future editions.

Kind regards,

Associate Professor Nick Cave
nickcave@animalhealthreview.co.nz

Independent commentary by Nick Cave.

Nick Cave is an Associate Professor in small animal medicine and nutrition at Massey University, NZ. He graduated from Massey University in 1990 with a BVSc, and worked in general practice for 6 years until 1997, when he returned to Massey for a residency in small animal internal medicine, attained membership in the Australasian College of Veterinary Scientists by examination, and graduated with a Masters in Veterinary Science in 2000. In 2004 he moved to the University of California, Davis, where he attained a PhD in nutrition and immunology. At the same time, he completed a residency in small animal clinical nutrition, and became a diplomate of the American College of Veterinary Nutrition by examination in 2004. In late 2005, he returned to Massey University to lecture in small animal medicine and nutrition. He is a founding member of the WSAVA Global Nutrition Committee, and a founding board member for the Massey University Working Dog Centre.

Using Companion Animal Research Review for CPD points

Reading relevant veterinary articles such as those in Companion Animal Research Review is a valuable way to keep current and can become part of your CPD record. Simply record the activity on your activity record and create a reflective record by writing a few sentences about what you learnt and how this impacts your practice as a veterinarian.

SEE THE VCNZ WEBSITE FOR TEMPLATES TO DOWNLOAD ACTIVITY RECORDS AND REFLECTIVE RECORDS **http://www.vetcouncil.org.nz/contProfDevel.php**

Tuberculosis due to *Mycobacterium bovis* in pet cats associated with feeding a commercial raw food diet

Authors: O'Halloran C et al.

Summary: These authors report on an investigation of an outbreak of tuberculous disease (due to *Mycobacterium bovis*) commencing with 6 young cats, living exclusively indoors in 5 different households across England, presenting to separate veterinarians across the UK. In addition to the 6 clinically sick cats, 7 in-contact cats were identified with proven evidence of *M. bovis* infection. Overall, 5 of the cats were either too sick to treat or deteriorated despite therapy (mortality rate 83%). Investigations revealed that affected cats with mycobacterial infections speciated to *M. bovis* were exclusively indoor cats and were fed a commercially available raw food product produced by a single manufacturer; other possible sources of exposure for these cats to *M. bovis* were excluded. The Food Standards Agency, Animal & Plant Health Agency, Public Health England and the food manufacturer concerned were notified/informed of this outcome.

Comment: I have no evidence to support the following claim: more harm has been caused by the raw food diet (RFD) craze through the feeding of nutritionally incomplete and unbalanced rations, than has been caused by specific enteropathogens present in raw food. I am frequently made aware of cases of rickets, osteopenia, fatty acid deficiency, vitamin D and E deficiency, folate deficiency, and iodine deficiency, yet infrequently aware of specific pathogen-associated disease linked to RFDs. Acute and chronic diarrhoea have been suggested and cases of listeria have been seen, but confirmed cases of enteropathogens from the food appear rare, relative to amount of contaminated food fed. However, it is the diet-derived infectious diseases that grip our attention. In Issue 7 of Companion Animal Research Review, I included a case series of polyneuropathies in dogs associated with RFD-derived *Campylobacter* species infections (Martinez-Anton L et al. 2018). And now, in the study by O'Halloran et al., we have a new concern. Or rather, an old concern, made new. The study hails from Edinburgh, and although it describes 11 cases of tuberculosis in cats, the authors have since diagnosed well over 100 cases from around the UK, of which they promise to tell more in the near future. The cases they have investigated were all fed food from a single manufacturer, who prided themselves on selling raw, wild-caught venison. "Natural Instinct" was the company, which has the comforting slogan "Cat food as nature intended", though nature would be a cruel mistress if she intends cats to eat tuberculosis-infested red deer. Tuberculosis in cats is rare, and the majority of cases present with localised nodular cutaneous disease, supposedly from hunting infected prey. So, it was unusual that in this case series the cats suffered from disseminated visceral forms, which the authors believe is consistent with the repeated ingestion of the organisms. In NZ, there are RFD-mongers promoting the supposed benefits of wild deer, pig, and possum diets, which is not only unjustified, but if the carcasses have not been appropriately inspected, positively irresponsible. It is difficult to dissuade some owners from feeding RFDs and even more difficult when their suspicions are raised by our profiting from selling alternatives. However, the very least we can do is to guide owners that insist on feeding RFDs to feed diets that have been properly formulated to meet the nutritional requirements, and produced by manufacturers that use products from the human food chains that have been inspected, and preferably air- or freeze-dried to kill parasites and reduce the bacterial load. Given the absence of evidence for any benefit of RFDs compared with the same product cooked and sterilised, we have a responsibility to speak up.

Reference: J Feline Med Surg. 2019;21(8):667-81
Abstract

Incidence and types of preceding and subsequent fractures in cats with patellar fracture and dental anomaly syndrome

Authors: Reyes NA et al.

Summary: The incidence of preceding and subsequent fractures to the patellar in cats with patellar fracture and dental anomaly syndrome were investigated in this study using data from the combined databases at the University of Bristol, UK, and Exclusively Cats Veterinary Hospital, USA. Among 191 cats identified with patellar fracture and dental anomaly syndrome, 92 cats (48.2%) had dental anomalies and 78 (40.8%) had fractures to other bones. In 21 cats (approximately 10%) the fractures were sustained preceding the patellar fractures and in 57 cats the fractures were sustained susequently. There were 175 fractures in total and the majority were characteristic of insufficiency (stress) fractures with a very similar configuration in each bone. The bones affected included the acetabulum (25%), tibia (22%), ischium (15.4%), humeral condyle (13.7%), calcaneus (5.1%), ilium (5.1%), pubis (3.4%), and other bones (10.2%). The authors concluded that the presence of such fractures should alert to the possibility that the cat is affected by patellar fracture and dental anomaly syndrome.

Comment: The other day, Ivayla Yozova, one of Massey's two erstwhile ECC specialists, incredulously berated me for using the term "sepsis", because apparently "it isn't used anymore". Do you ever feel like you just didn't get the memo? I know we can't know everything, but I do confess to lack immunity to the feeling I don't know anything at times. When I read of "knees and teeth syndrome" in cats, I thought, "Oh no, not again." As I write this, I will comfort myself with the warm blanket of delusion that I can construct by imagining I am not alone in my ignorance. Natalia Reyes is the lead author of this paper, however the syndrome owes its place in the veterinary literature to the last author, Professor Sorrel Langley-Hobbs, a surgeon at Bristol University. The syndrome, as she first described it in 2016, affects young cats, which present with the combined anomalies of retained deciduous teeth and transverse patella fractures, and it was affectionately christened "KaTS". This case series is the second publication of the syndrome and it has since morphed to be renamed "patellar fracture and dental anomaly syndrome"; from KaTS to PADS. This publication accretes a heterogenous collection of cases, of which only about half properly fitted the definition, since it included cases of patella fractures of all causes. Within the total, there is an interesting subset with histories of multiple spontaneous, non-traumatic fractures, often with radiographic evidence of precedent osteosclerosis. This sclerosis suggests prior remodelling and is interpreted by the authors as being indicative of "insufficiency fractures", a type of stress fracture, and probably resulting from mechanical failure due to a structural abnormality. Annoyingly, the paper does not report the dental abnormalities, and it is only in the discussion that they are referred to as "persistence of deciduous teeth and/or unerupted permanent dentition". Just as annoying, is the lack of speculation as to the pathophysiology, let alone cause. The authors made no mention of the diets of the cats, there was no discussion of possible genetic causes or correlates in human medicine, nor was there any hint as to what they propose as potential research avenues. For now then, all we can clearly conclude from this is that "PADS" exists, at least, in the UK it does. But do we radiograph the long bones of any cat with retained deciduous teeth? That seems excessive. Perhaps we should simply be aware that transverse patella fractures in cats are quite likely to be associated with a more generalised osseous anomaly, which may be a cause of other spontaneous fractures. Though what the owner can usefully do with that information, is beyond me.

Reference: J Feline Med Surg. 2019;21(8):750-64
Abstract

Assessment of the clinical accuracy of serum and saliva assays for identification of adverse food reaction in dogs without clinical signs of disease

Authors: Lam ATH et al.

Summary: The clinical accuracy of a saliva-based assay and 2 serum-based assays for detecting adverse food reaction (AFR) in healthy dogs was assessed in this study involving 30 healthy client-owned dogs. An online survey including comprehensive information about their pets' diet history was completed online by the owners. The immunoglobulin response to 24 foods was assessed in each dog via the 3 assays. Assays A, B (measuring food allergen-specific IgE concentrations in serum) and C (measuring food allergen-specific IgA and IgM concentrations in saliva) yielded positive results for 26, 18, and 30 dogs, respectively. A positive result to at least one assay was identified in all of the dogs and such a result was not significantly associated with prior food exposure. The median number of foods or ingredients to which dogs tested positive was 10.5 for assay A, 1 for assay B, and 12.5 (IgM) and 3 (IgA) for assay C. The authors concluded that saliva and serum assays for AFR often yielded positive results for apparently healthy dogs and are therefore not recommended for clinical use. Elimination diet trials remain the gold standard for diagnosis of AFR in dogs.

Comment: During my PhD ~~sentence~~ studies, I was interested in whether some aspects of food processing might increase the immunogenicity of dietary antigens. I was certainly not the first to detect salivary antibodies to food, though I may have been the first to detect them in cats or dogs. We found that the combination of cooking, emulsification, and the formation of maillard compounds created modified proteins that were more immunogenic than the uncooked proteins. In cats fed those diets, they produced salivary IgA to the modified proteins, or "neoantigens". I did not claim that this was a problem and certainly the cats were not allergic or in any way intolerant of the diets, but I speculated that in susceptible individuals, some types of food processing might increase the risk of food hypersensitivity. Given the prevalence of food hypersensitivity, it is obviously not a big risk, even if it is a risk. Since then Hemopet, a company in California, has started offering testing of food-specific antibodies in saliva, a test known as "NutriScan", and cite our paper as supportive of the concept. The company, led by the wildly heterodoxical and controversial Jean Dodds, states that NutriScan identifies "the commonly seen food intolerances and sensitivities in saliva. It is not a test for the rarely seen true allergies to foods." The company suggests that "High antibody levels indicate that the animal has a food sensitivity and intolerance to that food or foods". Recently, a mischievously sceptical veterinary dermatologist sent samples of saliva from healthy dogs, along with human saliva, rain water, and vodka, and was delighted to receive news of a series of food intolerances in all samples. Although the company reasonably cried "foul", and pointed out the effect on the ELISA that inappropriate samples might have, it did nothing for the confidence in the assay. Dr Dodds has recently published results of cases in dogs, and "1000 feline cases", claiming that "the novel salivary-based food sensitivity and intolerance test, described previously for canines, also provided a reliable and clinically predictive alternative to food elimination trials" (Dodds WJ. 2019) Given the absence of a gold standard, the absence of confirmatory food challenges, and no consideration of false results, neither of her studies can even approach an assessment of reliability. In fact, another partly independent evaluation of the utility of the test in experimentally sensitised and unsensitised control dogs, concluded that the test had no diagnostic utility. The present study by Lam et al., further underlines, highlights, and prints in gaudy flashing neon-lit font, the fact that the test is wholly without merit. The NutriScan test was positive in all 30 normal dogs, and supposedly identified between 4 and 24 antigens to which each of the dogs were intolerant. Since only healthy dogs were included, this study could only report the rate of false positives, which was 100%. However, false positives in adverse reactions to food are still problematic, and if the rate is 100%, the test is considerably worse than useless. The fact that perfectly healthy animals are spuriously identified as having a "dietary intolerance" does not deter the company, which argues that "NutriScan testing applies to healthy pets as well as those with known or suspected food reactivity, because saliva testing can reveal the latent or pre-clinical form of food sensitivity". In other words, they can never be wrong. Be aware that although this is a Californian company, they offer the diagnostic test worldwide, and you may be asked about it by clients. The answer is the simple, unfortunate fact that no test is superior to an elimination and challenge diet trial, and testing for salivary antibodies to food is worthless. When I am asked about it, I have the dual discomfort of wishing it didn't exist, and wishing I had nothing to do with it in the first place.

Reference: J Am Vet Med Assoc. 2019;255(7):812-6
Abstract

Effects of stylet-in versus stylet-out collection of cerebrospinal fluid from the cisterna magna on contamination of samples, sample quality, and collection time

Authors: Shamir SK et al.

Summary: The safety and efficiency of stylet-in and stylet-out techniques for the collection of CSF from the cisterna magna was assessed in this prospective crossover study involving 10 adult purpose-bred research Beagles. CSF samples were obtained from anesthetised dogs using either technique and these were processed within 1 hour of collection; 2 weeks later the other sample collection technique was performed. Stylet-in samples contained higher numbers of cellular debris, but this did not affect sample quality. The stylet-out technique was the more rapid of the 2 techniques. There were no adverse effects observed for either technique.

Comment: When I was at school, I received a Valentine's card from a girl I had fancied for ages, perhaps even longer than a week. On receipt of the card, my heart leaped in my chest like a spawning salmon, and my hands moved with a chaotic disregard of cerebella control as I tore open the envelope, pausing briefly to smell it, and then to consider licking the part she had licked. Inside the card, written in a precociously beautiful cursive script, were the words, "Please leave me alone, I don't like you in that way". Or words to that effect. To be honest, I don't remember precisely what was written, but I do remember vividly the heady mixture of surprise, disappointment, embarrassment, and annoyance that she had taken the trouble to tell me that so formally. I get a taste of that same emotional smorgasbord when I receive results from the laboratory and read the words "non-diagnostic sample", usually accompanied by the cheerfully unhelpful offer of talking with the pathologist should I want to. Who hasn't aspirated blood instead of tumour, squashed cells into a degenerate quagmire, forgotten to agitate a blood sample before it clots, left a sample too long before submitting, or just plain stuck the wrong bit? The stakes are highest for samples collected under anaesthesia, and especially if it incurs a risk to the patient. CSF sampling is a canonical example. I was taught by Professor Boyd Jones, who told me to use the stylet-out technique, assuring me it would produce the best sample, and I have not had reason to change yet. Immediately after penetrating the skin, the stylet is removed, and the "open" needle is slowly advanced into the cisterna magna, or lumbar site, until CSF flows through the needle hub and is caught by an attentive tube holder while the needle is held in place. The study by Shamir et al., is simple, elegant, and though not in contention for next year's Nobel Prize, is a very useful answer to the question of whether leaving the stylet in might reduce contamination of the sample. The fact that the answer is "no", is another demonstration of the wisdom of Boyd. In fact, the repeated removal and replacement of the stylet actually resulted in a higher rate of contamination and significantly increased the risk of diagnostic uncertainty. Thus, for once, I can continue to do as I have always done, and know that in so doing, I am minimising the risk of receiving another disappointing communication.

Reference: Am J Vet Res. 2019;80(8):787-91
Abstract

Use of the Health Belief Model to identify factors associated with owner adherence to elimination diet trial recommendations in dogs

Authors: Painter MR et al.

Summary: Factors associated with owner adherence to elimination diet trial (EDT) recommendations by veterinarians for dogs with suspected cutaneous adverse food reactions (CAFRs) were investigated using the Health Belief Model. Review of medical records between April 2012 and April 2017 from a single veterinary dermatology specialty practice identified 665 owners of dogs prescribed an EDT. A total of 192 of the owners completed an anonymous online survey developed on the basis of the Health Belief Model. Among the 192 respondents, 77 (40.1%) reported 100% adherence to EDT recommendations, and 115 (59.9%) reported < 100% adherence. The odds of owners reporting 100% adherence to EDT recommendations were significantly decreased by owner's perceptions of barriers (adjusted OR 0.86) and were significantly increased by self-efficacy or confidence in performing an EDT as directed (adjusted OR = 1.18), and by owner knowledge regarding diets and CAFRs in dogs (adjusted OR 1.30).

Comment: The motivation to use an alternative test to dietary elimination-challenge trials to diagnose adverse food reactions is clear: diet trials are a pain. Part of the pain arises from poor client compliance, or at least, the uncertainty as to whether the owner complied, and whether your conclusions from the test are valid. Thus, it is important that we understand the reasons for failure to comply, and perhaps identify those owners who are at risk so we can intervene to improve the compliance rate. In the study by Painter et al, the authors wanted to add to our understanding by looking for associations between their answers to the "Health Belief Model" questionnaire, and whether they were 100% compliant with a prescribed diet trial. On reflection, it does seem optimistic that their approach, albeit well meaning, would yield useful results. Firstly, the study population was owners of animals subjected to diet trials, who had sought referral for their animal. We can only speculate as to the difference between that population and "all pet owners", but I have confidence that they are different in significant ways, at the very least in terms of motivation and wealth. The 665 owners were asked to participate in the survey, and a third complied. Anyone see the irony? It seemed the authors didn't think it worth commenting on, but surely the subset that participated was a non-random sample of the original, biased population. The time between the diet trial and participation in the study was between at least 3 months, and 5 years. What is the chance that recall of compliance is accurate 5 years after the trial? And on top of that, there is the inherent inaccuracy and bias of answering the principle question of whether they were 100% compliant. Yet despite all those limitations, 60% confessed to being less than perfect, which is definitely what I would be. Or am. The authors tested the association between the owners' compliance and their answers to questions about their knowledge of adverse food reactions, belief that it was the cause, severity of the signs, perceived benefits of the trial, perceived barriers, assessment of self-efficacy, and their feelings of social support. Is it surprising that people who are conscientious and do not perceive barriers to participation were the most compliant? One might argue that those findings are axiomatic. But the finding that an understanding of adverse reactions to food was associated with self-reported compliance was more interesting. Research in human medicine has shown that understanding is an important factor for eliciting changes in health-related behaviours of patients. There is little reason to believe it is not the same for pet owners. Although I suspect most of us hope that clients understand the reasons for our prescriptions, data in human medicine suggests it is frequently not the case. In this study, we have a small piece of evidence that emphasises the risk that a lack of understanding by our clients has.

Reference: J Am Vet Med Assoc. 2019;255(4):446-53
[Abstract]

Antiviral activity of itraconazole against type I feline coronavirus infection

Authors: Takano T et al.

Summary: In domestic and wild cats, feline coronaviruses (FCoVs) are the causative agents of severe systemic disease (feline infectious peritonitis [FIP]). These authors investigated the antiviral activity of itraconazole for the treatment of type I FCoV infection, the most dominant type world-wide (approximately 70-90% of cases). Itraconazole inhibited type I FCoV infection and also exhibited antiviral effects in cells after viral infection.

Comment: Are you surprised to read of someone considering itraconazole as a therapy for FIP? Is the needle on your sceptometer in the red? Desperate times lead to desperate measures, and desperation is certainly the dominant feeling when diagnosing FIP, so it is understandable that all manner of therapies have been tried. Specific antiviral drugs such as the nucleoside analogues acyclovir, zidovudine, and ribavirin were obvious choices, but lack of efficacy or toxicity in cats has ruled out candidates to date. "Immunostimulants" appear popular with some, though it has always bemused me as to why one would think that a disease dominated by a systemic inflammatory response would benefit from more stimulation. Immunosuppression with steroids is the most widely accepted therapy, though there are clearly some cats that do not respond at all. At the moment, the drug with the greatest promise is the thrillingly named "GS-441524", a new nucleoside analogue (Pedersen NC et al. 2019). The promise of a product licensed to use in cats is not on the horizon, although it can be purchased as a "chemical", at a cost of about $100/mg. At a daily dose of 6-16 mg per cat, it almost seems insulting to mention. So, what else can we offer? Well, over the past few years, it has become apparent that enveloped viruses (those that keep some of the host cell membrane as a cover following replication) are affected by alterations in cellular cholesterol metabolism. The cholesterol content of the viral envelope affects the ability of the virus to fuse to a host cell, and thus viral entry can be inhibited by decreasing cholesterol availability. In humans, cholesterol transport inhibitors, statins, and other drugs that affect lipid metabolism can affect viral replication and have been shown to reduce viral loads in HIV and hepatitis C infection. It is intriguing to learn that during viral infections, γIFN stimulates the production of a cholesterol metabolite, 25-hydroxy cholesterol (25-OH chol), which disrupts enveloped virus replication, and interferes with viral envelope fusion with cells. Nature shows the way, and 25-OH chol is being investigated as an anti-viral compound. Itraconazole, and other azoles, are not cholesterol analogues, but they work by inhibiting ergosterol synthesis, which is required for fungal cell wall synthesis. In mammals, azoles also inhibit cholesterol synthesis and decrease total serum cholesterol and LDL in humans by up to 20%. So, it is not so desperate to consider if itraconazole might inhibit the replication of FCoV. In the study by Takano et al., they showed that there was indeed significant inhibition in cell culture, at a concentration of 2.5 μM. Dosing cats with 10 mg/kg bid results in plasma concentrations of approximately 4.8 μM. So, are you still sceptical? Perhaps we still should be, since inhibition was only partial, it was only effective against Type 1 FCoV, and although at least 75% of FIP cases are due to Type 1 worldwide, we don't know what proportion of Type 1 and Type 2 we have in NZ. Nonetheless, I cannot think of any reasonable argument against the off-label use of itraconazole at a dose of 10 mg/kg bid, perhaps with prednisone as well, with the hope it may slow viral replication and prolong a reasonable quality of life, especially in non-effusive cases. It seems less desperate than anything else we have at the moment.

Reference: Vet Res. 2019;50(1):5
[Abstract]

Assessment of the efficacy of firocoxib (Previcox®) and grapiprant (Galliprant®) in an induced model of acute arthritis in dogs

Authors: de Salazar Alcalá AG et al.

Summary: This randomised, two-sequence, assessor-blinded study investigated the potency and persistence of acute pain control over 24 hours resulting from a single oral dose of either firocoxib (Previcox®) or grapiprant (Galliprant®) in an acute induced canine arthritis model. The study comprised 2 separate experiments. In the first experiment, the mean post-arthritis induction (PAI) lameness ratios in firocoxib recipients remained at or above 0.80, while in grapiprant recipients, ratios were 0 at 5 and 7 hours PAI (7 and 9 hours post-treatment), and 0.16 at 10 hours PAI (12 hours post-treatment). Control and grapiprant group lameness ratios were significantly lower at each PAI assessment ($p \leq 0.026$ and $p < 0.001$, respectively) relative to the firocoxib group, except at 1.5 hours PAI, at which time acute pain was still not installed in untreated control dogs. In the second experiment, the mean lameness ratios for the controls were 0 at 3, 5 and 7 hours PAI, and 0 in grapiprant recipients at 5, 7 and 10 hours PAI (i.e., 19, 21, and 24 hours post-treatment). The lowest mean lameness ratio in the firocoxib recipients was 0.36 and occurred at 3 hours PAI (i.e., 17 hours post-treatment). The lameness ratio differences between the firocoxib and both the control and grapiprant groups were significant at all assessments ($p \leq 0.033$ for both groups), except at 1.5 and 3 hours PAI (i.e., 15.5 and 17 hours post-treatment), due to the needed time for pain to install in the untreated control dogs. There were no significant differences detected between the grapiprant and control groups in either experiment.

Comment: At several veterinary conferences these days, you are asked to either precede, or succeed your talk with a "declaration of interest". I have never heard a cogent argument for what this ritual achieves, though the glib explanations suggest the exponents believe it reduces the risk of falsehood, or alerts the listener to the possibility of bias. My thought remains that we should subject every scientific presentation to the same scepticism and critical evaluation, whether the person presenting it has an obvious interest or not. Something is either true or false, but it is neither simply because someone has declared or withheld a vested interest. And do those that argue for the declaration believe the antithesis then holds? That when eminent academics without a taint of commercial interest in their souls announce something is so, we can accept it thus, without question? To the study by García de Salazar Alcalá et al. "Grapiprant" is not, as the name suggested to me, an undergarment for groping enthusiasts, but a prostaglandin-receptor antagonist. Specifically, it blocks signalling via the EP4 receptor, which is the most important of the 4 known receptors that PGE2 binds to. Blocking the EP4 receptor has obvious appeal, because it is responsible for sensitisation of nociceptive fibres, for PGE2-elicited vasodilation and increased permeability, and is expressed on T and B lymphocytes, macrophages, and dendritic cells. In addition, protection of the GI mucosa is only partially dependant on EP4 receptors, so it might be expected that blocking the receptors will cause fewer GI side effects than COX-inhibition. The first assessment of grapiprant in dogs was a large, placebo-controlled study of 262 dogs with osteoarthritis (Rausch-Derra L et al. 2016). The outcome measures were owner and vet subjective assessment scores, and as so often happens with osteoarthritis trials, the placebo group improved somewhat, but there was a marginally greater improvement in the grapiprant group. That first study was conducted and written up by the manufacturer, Aratana Therapeutics, and was published in the JVIM accompanied by a declaration of a conflict of interest. The authors in this study by García de Salazar Alcalá et al., hail from a private research contractor, and from Boehringer-Ingelheim, the manufacturers of Previcox®. The two studies differ in many ways, not the least of which is that the first was a study of naturally occurring osteoarthritis, and the study here was a urate crystal-induced model of acute arthritis. In this study, the analgesia from firocoxib was apparently far superior to that from grapiprant, which looked little better than the placebo in all the outcome measures. Are the startlingly different conclusions in the two studies only a result of the differences in the study subjects? Could grapiprant be effective in osteoarthritis, but not in acute arthritis? Or should we treat one, or both of these studies with increased scepticism because of the vested interests? I can't tell. Time will though.

Reference: BMC Vet Res. 2019;15(1):309
Abstract

Cardiac effects of a single dose of pimobendan in cats with hypertrophic cardiomyopathy; A randomized, placebo-controlled, crossover study

Authors: Oldach MS et al.

Summary: These authors investigated the cardiac effects of pimobendan in cats with hypertrophic cardiomyopathy. Thirteen purpose-bred cats with naturally-occurring hypertrophic cardiomyopathy (HCM) due to a variant in myosin binding protein C were randomised to receive either oral placebo or 1.25 mg pimobendan 1 hour prior to complete standard echocardiography; the following day, they were crossed over and received the remaining treatment. Treatment with pimobendan resulted in a significant increase in left atrial fractional shortening compared with placebo (41.7% vs 36.1%; $p = 0.04$). No significant differences were seen between pimobendan and placebo in left ventricular outflow tract (LVOT) velocities (2.8 m/s vs 2.6 m/s) or the number of cats with LVOT obstructions (12 vs 11). Systolic measures, including left ventricular fractional shortening, mitral annular plane systolic excursion, and tricuspid annular plane systolic excursion did not differ between the treatments.

Comment: When it was first suggested that pimobendan might be effective in managing feline HCM, it seemed strange and counterintuitive. In fact, the reasons to suspect it might be effective were no more compelling than those to suspect it might be a terrible idea. Clearly the arterial and venous dilation would be helpful, especially in cats with congestive heart failure, but there were very real concerns that the inotropic effect might exacerbate any left ventricular outflow obstruction, might increase myocardial strain, and at best be counterproductive, and at worst, detrimental. Nonetheless, the first published use in feline HCM in 2011, was a retrospective case series of 170 cats of which 68 had HCM (MacGregor JM et al. 2011). Given the absence of controls, the study could not detect any positive benefit, though pleasingly, the authors didn't suggest there was one, only concluding that it didn't appear to make them worse. It is often claimed that pimobendan increases the contractility without increasing the myocardial oxygen demand. To be honest, I've never understood why that claim is made, especially given that the paper purported to support the claim, specifically found the opposite, and showed that the increase in O_2 utilisation was the same as that of dobutamine (Hata K et al. 1992). So, it is reasonable to posit that pimobendan might increase myocardial workload, and thus to test whether it is beneficial, or detrimental, in feline HCM. `The paper by Oldach et al., is the first to carefully evaluate the drug in cats with HCM. They used a colony of Maine Coons at UC Davis with a well described, heritable form of HCM. It was rigorously conducted and the echocardiographic measurements were extensive, and probably only possible with the butorphanol/acepromazine sedation. It's not often that we measure left atrial contractility but, interestingly, it was that, and not the ventricular contractility that was affected by the single dose. Not only might that effect improve LV filling, but it could also reduce the retention of blood in a dilated atrium, and decrease the risk of thromboembolism. To allay fears somewhat, there was no overall exacerbation of pre-existing outflow tract obstruction, although it was a small study and one cat did deteriorate, and another developed systolic anterior mitral valve motion. Despite increasing systolic function in healthy dogs and cats, it was not found to in these cats with HCM. Therefore, the net effect of peripheral vasodilation, atrial contraction and an apparent absence of adverse effects is promising support for its use in cats with HCM, with or without congestive heart failure.

Reference: Front Vet Sci. 2019;6:15
Abstract

CLICK HERE **to read previous issues of Companion Animal Research Review**

Decrease in population and increase in welfare of community cats in a twenty-three year trap-neuter-return program in Key Largo, FL: The ORCAT Program

Authors: Kreisler RE et al.

Summary: This retrospective study evaluated the effect of the 23-year trap-neuter-return (TNR) program in Key Largo in the Florida Keys (The ORCAT Program), on the population size of community cats in the Ocean Reef Community. Cat census data collected between 1999 and 2013, and individual medical records for cats whose first visit occurred between 3/31/1995 and 12/31/2017 were included in the analysis. The free-roaming population decreased by 55% from 455 cats in 1999 to 206 in 2013 ($p < 0.0001$). A total of 3487 visits were recorded for 2529 community cats, with 822 orchiectomies and 869 ovariohysterectomies performed. A total of 1111 cats were returned back to their original location and 1419 cats were removed via either adoption (510), transfer to the adoption centre (201), euthanasia of unhealthy or retrovirus positive cats (441), death in care (58), or they were dead on arrival (209). Between 1995 and 2017 there was an 80% reduction in the number of first visits per year (348 vs 68). The estimated average age of the active cat population increased by 0.003 months per year ($p = 0.031$) from 16.6 months in 1995 to 43.8 months in 2017. There was also a 1.9 month per year increase in the mean age of cats at removal ($p < 0.0001$), from 6.4 months in 1995 to 77.3 months in 2017; however, the mean age of cats at return to the original location did not change over time and remained at 20.8 months. Overall, the prevalence of retrovirus was 6.5%, with FIV identified in 3.3% of cats and FeLV identified in 3.6%; this prevalence decreased by 0.32% per year ($p = 0.001$), with FIV decreasing by 0.16% per year ($p = 0.013$) and FeLV by 0.18% per year ($p = 0.033$). The authors concluded that this long-term trap-neuter-return program achieved a decrease in the community cat population and an increase in population welfare as measured by a decreased retrovirus prevalence and an increased average age.

Comment: There are few things more divisive amongst welfare advocates than TNR programs for cats. The advocates speak of the welfare of the cats, whilst, like the Lorax, the critics speak – well not for the trees, but for the critters that live in them. The general points for consideration are the welfare of the cats, the welfare of the prey, and whether it is an effective strategy for reducing a stray population over time. During our studies of feral cats on Ponui Island in the Hauraki Gulf, we found that 97% of kittens born don't make it to breeding age, and death is often due to predation from other cats (Strang KE. 2018). That means a population is spinning its wheels reproductively and there is a massive capacity for replacement when individuals are removed. But it also means that a closed population might be successfully controlled over a couple of generations of cats, with a sufficiently-intensive TNR program. On the other hand, recruitment of fertile individuals into a more open population can occur quickly, especially from the periphery, which partly explains why studies of the efficacy of TNR programs are not concordant. In the study by Kreisler et al., the study area is a restricted location on the northernmost tip of Key Largo in the Florida Keys. A reduction of 50% in 14 years seems pretty reasonable and the population there had few immigrants. On the other hand, for those focused on a more rapid reduction, it would seem slow, and there is the possibility that it had plateaued, and there is no guarantee of eradication. In addition, the estimated age of the cats was clearly decreasing over the last 10 years of the study, which speaks against population control. The drop in retroviral prevalence is consistent with the reduction in fighting intact males, although the authors did take a generous view of welfare, and were happy to use retroviral prevalence as an index thereof. And it's that last bit that I feel uncomfortable about. How does one quantitatively assess the welfare of a feral cat population? Should the weighing be the health of a TNR-managed population, against the health of an unmanaged population? That seems the wrong equation to me. Though apparently harsh, the act of trapping and euthanasing a cat is not immediately different from trapping and anaesthetising for neutering. If the population is eliminated through a trap and euthanase program, then the absence of suffering in cats that do not exist weighs heavily against even a well-managed population. These are not easy questions, but in NZ where we have to consider the ecological as well as welfare costs of predation by feral cats, I find I'm on the side of the Lorax, and speak for the critters that live in the trees, and the results of this study have not swayed me in favour of TNR programs.

Reference: Front Vet Sci. 2019;6:7
Abstract

Differences in boys' and girls' attachment to pets in early-mid adolescence

Authors: Muldoon JC et al.

Summary: Data from the 2010 Health Behaviour in School-aged Children survey in Scotland were used to examine various qualities of 2472 adolescents' attachments to their pet dogs, cats and small mammals. The adolescents answered pet ownership questions and completed the 'Short Attachment to Pets Scale'. A pattern of weakening attachment to pets was observed with increasing age, with girls giving higher ratings for emotional support qualities of attachment, and stronger attachments evident with dogs.

Comment: When are gender differences meaningful, or relevant? When is it appropriate to account for them, and when does consideration border on sexism? The gradual gender shift that has occurred in our profession over the past 30 years has led to some interesting changes. But when do we stop talking about that and just talk about "the profession"? In an online survey of almost 7000 cat owners from around the world that we recently published, 92% were female. Is that surprising, relevant, meaningful? Does that limit our inferences to "all cat owners"? The benefits of pet ownership are now well established, but is the difference in gender attitudes important? The authors of this paper clearly think it is. They conclude with the statement that it is "important that we understand the facilitative and protective functions of animals as we transition through different life stages". They argue strongly for the roles that pets can have in providing companionship, a sense of emotional support, and how they can reduce anxiety and improve social cohesion. But are the gender differences important in that regard? The authors calculated the effect size of the gender differences and the greatest effect size they found (partial eta-squared, for the stat geeks) was 8%. That means that of the variation in responses between children, only 8% was explained by their gender difference. For most of the measures, it was less than 4%. So, whilst it is a statistical difference, it just doesn't seem to me to be a meaningful one. In fact, it may be counter-productive or even prejudicial to suggest that "girls form stronger attachments to pets than boys", because for many, that is not the case. Given the wide variety of humanity, it may be a better strategy to ignore small effects from gender than to highlight them. When my kids were younger, I "demonstrated" how to use a jump that I had constructed on a steep driveway for their scooters. My first, and only attempt, ended with me landing on my back, with the scooter in my face. My daughter rushed up to me, tearfully concerned for my welfare. My son remained standing at the top of the driveway, strangely bent over with his hands clutched in his crotch. When I later hobbled up to ask him why he hadn't checked up on his old man, he apologised, and explained that he would have done, were it not that he was laughing so much he had to squeeze the end of his penis so he didn't wet his pants. I cannot help but interpret that to be a meaningful gender difference.

Reference: J App Dev Psych. 2019;62:50-8
Abstract