WHAT'S NEW IN CLINICAL PHARMACOLOGY?   **CLINICAL PHARMACOLOGY**
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Introduction
The search for new therapeutic options and the use of multiple drugs in the management of diseases in companion animals is increasing. Years of research and significant financial investment are devoted to bringing new animal drugs to market. These research efforts have resulted in the approval of several new veterinary drugs that have addressed some of the unmet needs of clinical practice. In addition, there has been new research with drugs used in dermatology, pain management, and antimicrobial therapy.

Topics
   Update on antimicrobial therapy
   Use of antihistamines in practice
   Antiemetic therapy
   New advances in pain management

Within this manuscript, recommendations for medical treatment may be covered that are not labeled for use in dogs and cats. Whether these are products developed for use in humans or are extra-label use of veterinary products, the recommendations are based on medically recognized standards of care.

Update on Antimicrobial Therapy
Antimicrobial agents are one of the most commonly prescribed drugs in veterinary medicine. Beta lactams are time dependant antimicrobials, and efficacy is related to the time above the minimum inhibitory concentration (MIC) (T >MIC). For this class of drugs, it is recommended that the concentrations remain above the MIC for at least 50% of the dosing interval (Turnidge 1998; Craig 1998). For antimicrobials with twice daily dosing, this can often be achieved if the owner is compliant in giving the medication every 12 hours, the organism is susceptible to the drug, and an appropriate dose is administered. If the owner is noncompliant, then there are long windows of time in which the drug concentrations fall below the MIC during the dosing interval. In theory, this repetitive behavior over time may lead to treatment failure. In human medicine, studies have shown if injectable beta lactams are administered as an infusion rather than as a bolus injection, the T>MIC is maximized, and this correlates with improved treatment outcomes and reduced costs (Gillespie et al. 2005). Obviously, administering infusions to our veterinary patients is not always practical, and ideally we want to treat them as outpatients. To optimize the T > MIC, a drug or a dosing regimen that maintains concentrations above the MIC for the majority of the dosing interval should be selected. There are a few drugs labeled for once daily administration, and these regimens have shown to increase compliance in human and animal studies (Barter et al. 1996). Examples of oral drugs labeled for once a day administration in small animals include fluoroquinolones (marbofloxacin, enrofloxacin, difloxacin, orbifloxacin), cephalosporins (cefpodoxime proxetil, ceftiofur sodium, cefadroxil (cats)), and sulfonamides (sulfadimethoxine and sulfadimethoxine/ormetoprim). All parenteral and oral antimicrobials approved prior to 2008 for dogs and cats require dosing regimens of at least once a day administration. Parenteral drugs that have to be administered multiple times a day are often not appropriate for outpatient therapy. There are several long acting injectable antimicrobial drugs labeled for large animals aimed to increase the convenience of administration while providing good activity against susceptible pathogens. Cefovecin is the first long acting cephalosporin approved for use in dogs and cats. Cephalosporins are one of the most frequently prescribed antimicrobials to treat skin infection in dogs and cats. Cephalosporins have the advantage of being bactericidal, being resistant to hydrolysis by inactivating enzymes, and having a good safety profile, and they have good efficacy against the most common pathogens found in skin infections. Cephalosporins currently used for skin infections and examples of dosing regimens include cefpodoxime proxetil (5–10 mg/kg once a day), cephalexin (22 mg/kg every 12 hours), and cefadroxil (22 mg/kg every 12 hours). Cefovecin is approved for the treatment of superficial pyoderma, abscesses, and wounds caused by susceptible strains of *S. intermedius* and *S. canis* (Group G) in dogs and for the treatment of abscesses and wounds caused by susceptible strains of *P. multocida* in cats. The label dose is 8 mg/kg subcutaneously, and a single injection provides up to 14 days of antibiotic treatment in dogs and cats. A second subcutaneous injection may be administered in dogs if the response to therapy is not complete. Cefovecin injectable is an aqueous solution and has rapid and complete absorption after a subcutaneous injection (Stegemann et al. 2006a). The long half life of the drug (5.5 days in dogs and 6.9 days in cats) is primarily attributed to high protein binding. Cefovecin addresses the compliance issues we encounter in practice and provides an uninterrupted period in which the concentrations are above the MIC for

susceptible bacteria for several days (Stegemann et al. 2006a, 2006b). In the United States field efficacy studies a single injection of cefovecin was clinically equivalent to a 14-day dosing regimen with cefadroxil (Six et al. 2008).

Use of Antihistamines in Practice
Antihistamines have been used in combination with other drugs to manage pruritus for many years. Specifically, H1 receptor antagonists are classified into first and second generation groups. Examples of first generation H1 receptor antagonists include chlorpheniramine, hydroxyzine, clemastine, trimeprazine, and diphenhydramine. Side effects of the first generation H1 antagonists reported in people include sedation and antimuscarinic effects (dry mouth, blurred vision, urinary retention). Second generation H1 antagonists are non-sedating and examples include loratadine, desloratadine, cetirizine, and fexofenadine. Antihistamines block the inflammatory effects of histamine. Despite the widespread use of these products in veterinary medicine, there is a lack of pharmacokinetic, efficacy, and safety studies in companion animals. Dosages are extrapolated from human medicine, and efficacy is largely based on a few studies and anecdotal reports. The efficacy of antihistamines for the management of pruritus and inflammation in dogs has been uncertain. In a study by Zur et al. (2002), hydroxyzine and diphenhydramine were the most often prescribed, and good response was seen in approximately 54% of dogs. In people, most of the antihistamines have half lives that support one or twice a day dosing. Few pharmacokinetic studies have been performed in dogs to determine appropriate dosages and dosage intervals.

There have been a few pharmacokinetic studies investigating the bioavailability of antihistamines in dogs. A study with clemastine demonstrated only 3% of the administered dose (0.5 mg/kg) was available in the systemic circulation (Hannson et al. 2004). Systemic availability after oral administration of chlorpheniramine has been in the range of 9.4–39% depending on the dose (Athanikar et al. 1979). Recently, the pharmacokinetics of hydroxyzine were investigated in dogs and compared with the effect of the drug on inhibition of wheal formation induced by intradermal injections of histamine (Bizikova et al. 2008). After an oral dose of 2 mg/kg, the bioavailability was 75%, and hydroxazine was rapidly converted to the active metabolite cetirizine (Bizikova et al. 2008). Maximum inhibition of wheal formation occurred during the first 8 hours. These results support a twice a day dosing regimen.

Maropitant
Vomiting stimuli can originate from many difference sources (vestibular apparatus, chemoreceptor trigger zone, gastrointestinal tract, higher brain centers), but all stimuli ultimately converge at the emetic center to initiate the vomiting reflex. There are a variety of antiemetics available that act at different parts of the vomiting pathways (metoclopramide, chlorpromazine, 5HT-3 antagonists, aminopentamide). Maropitant is a broad spectrum antiemetic approved by the FDA in 2007. Maropitant blocks neurokinin-1 (NK-1) receptors in the emetic center and CRTZ and therefore has the ability to block vomiting stimuli from all incoming sources. Recently, maropitant was investigated in cats, where it showed good efficacy when vomiting was initiated by xylazine or motion, and it was well tolerated (Hickman et al. 2008).

New Advances in Pain Management
Over the last several years recognition of pain in animals and the need for pain management has increased dramatically. Incorporation of pain monitoring techniques and pain management protocols into practice is important. However, protocols are a guide only, and pain management should be customized to the patient and the procedure.

Osteoarthritis is the primary cause of chronic pain in dogs, and management often requires a multimodal pain management approach. Since 24–34% of animals are obese or overweight (Burkholder et al. 1997), diet and nutrition play an important role in pain management. Weight loss has been shown to improve clinical lameness in overweight dogs with hip osteoarthritis (Impellizeri et al. 2000). Nonsteroidal anti-inflammatory drugs have historically been the initial analgesic of choice in the management of pain associated with osteoarthritis. However, when pain progresses or when NSAIDs are contraindicated, other analgesic options are needed. Oral opioids are frequently used for chronic pain management in people. Unfortunately, in dogs most oral narcotics are poorly absorbed and the half life is so short that they have to be administered every 2–6 hours. Other examples of oral drugs used as an adjuvant in pain management include tramadol, corticosteroids, amantadine, gabapentin, and amitriptyline. Dosages, efficacy, and safety of the latter three have primarily been based on anecdotal reports.

Tramadol is a centrally acting analgesic drug that has been used off label in veterinary medicine frequently in combination with other analgesics in the pain management of osteoarthritis and other painful conditions. Pharmacokinetic studies by Kukanich & Papich (2004) showed tramadol had good absorption after oral

administration and recommended an initial dosage of 5 mg/kg every 6 hours. Other advantages of tramadol are that it is not controlled and is well tolerated, with few adverse effects.

Amantadine is indicated for the prophylaxis and treatment of signs and symptoms of infections caused by various strains of influenza A virus, treatment of Parkinsonism, and drug induced extrapyramidal reactions in people (reference: package insert for Symmetrel). Evidence suggests through inhibition of NMDA responses, amantadine is effective in treating nervous system disorders (Blanchet et al. 2003). Dose recommendations have been 3–5 mg/kg every 24 hours for dogs and cats (Tranquilli et al. 2004). Recently information was published on the use of amantadine in combination with an NSAID to improve pain relief in dogs with pelvic limb lameness (Lascelles et al. 2008). Results of the study suggest dogs with osteoarthritic pain refractory to an NSAID had improved physical activity after amantadine was added to the regimen for 21 days (Lascelles et al. 2008).

Transmucosal buprenorphine. Buprenorphine is a partial opioid mu agonist. Most opioids are not well absorbed after oral administration to dogs and cats. The bioavailability of oral buprenorphine in dogs is 3–6 % (Garrett et al. 1990). Transmucosal administration of buprenorphine to cats was investigated, and the bioavailability was determined to be 116% (Roberston et al. 2005). Today, many practitioners utilize this delivery technique to provide analgesia to cats after surgery and for other painful conditions. Advantages include good systemic absorption, easy administration, and ability to treat animals as outpatients. A recent study looked at the pharmacokinetics of the injectable formulation of buprenorphine (0.3 mg/mL) administered after intravenous and transmucosal administration in healthy dogs (Abbo et al. 2008). The bioavailability range was 38–47% after a range of doses. The transmucosal route of administration was well tolerated in dogs, with sedation and salivation being the most common side effects (Abbo et al. 2008).

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