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PHARMACOTHERAPEUTICS IN EXOTIC SMALL MAMMALS: AN UPDATE AND A REVIEW

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Introduction

Pharmacokinetic studies in exotic small mammals are lacking and, therefore, most of the dosages used in these species are based on empirical data, observations, and experience. Because drug uptake depends on factors such as age, sex, physiology, disease state, diet, etc., it is important for us as veterinarians to know some of the pharmacobiologic, physiologic, and anatomic characteristics of these species. It should also be noted that most of the drugs used in exotic small mammals are extralabel. This review outlines drug administration sites, compounding, and some of the issues involved in selecting an antibiotic, analgesic, or nonsteroidal, anti-inflammatory drugs for use in exotic small mammals.

Compounding

Exotic animal practitioners face daily challenges to meet the pharmaceutical needs of their small mammal patients. Because there are few approved medications for use in these patients, attempts to meet these challenges include: extralabel use of human and domestic animal products; compounding by the practitioner; use of compounding service; using medicated feeds; and using imported pharmaceutical productions. There may be both legal and ethical issues that the practitioner must be aware in using any of the aforementioned strategies.

Antibiotics

Antibiotics are probably the most commonly used medications in small mammal medicine. Because pharmacokinetic studies are lacking in these pet species and are often empirical, it is helpful to know the basic pharmacologic features and the side effects of the drugs being used for maximum safety and efficacy.

Because rabbits are herbivorous animals, their intestinal microflora consists mainly of gram positive bacteria and anaerobic bacteria. Antibiotic choices in rabbits, however, are limited because many antibiotics suppress the healthy flora and allow pathogens to proliferate, resulting in well documented enteric disorders. Antibiotics which have been reported to cause dysbiosis/enteritis/enterotoxemia in rabbits include amoxicillin, amoxicillin/clavulanic acid, ampicillin, cephalosporins, clindamycin, erythromycin, lincomycin, and penicillin[1]. There have also been some reports of antibiotic related colitis in rabbits given penicillin/streptomycin, trimethoprim/sulfamethoxazole, tetracycline, tylosin, and gentamicin. It should also be noted that, in some cases, enteritis can develop weeks after the antibiotic has been discontinued. Oral use of these medications generally is contraindicated in rabbits; however, penicillin is occasionally used parenterally on a limited basis[2].

Unfortunately, there is a lack of data (based on clinical trials) on the use of most antibiotics in rabbits. Very few antibiotics have been evaluated for their therapeutic effectiveness, and, therefore, dosages in rabbits often rely largely on empiric data. Antibiotics that are generally considered safe in rabbits include the fluoroquinolones, sulfonamides, chloramphenicol, and metronidazole. Antibiotics that do not cause problems with normal usage can cause diarrhea when given in large doses.[2] Even when presumably "safe" agents are used, rabbits on antibiotics should be monitored for signs of gastrointestinal distress.

Inappropriate antibiotic treatment can also result in enteritis and antibiotic-associated clostridial enterotoxemia in rodents, especially when antibiotics with a primary gram-positive spectrum are given. Incidence is higher when agents are given orally. Chinchillas, guinea pigs, and hamsters are most susceptible. Also, direct toxicity from streptomycin and dihydrostreptomycin occurs in gerbils, guinea pigs, hamsters, and mice. Procaine, included in

some penicillin preparations, can be toxic to mice and guinea pigs. Guinea pigs and chinchillas are highly susceptible to the ototoxic effects of chloramphenicol and aminoglycosides at dosages above those recommended clinically. Antibiotics implicated in antibiotic associated clostridial enterotoxemia in rodents include:[1]

- Chinchillas: penicillins (including ampicillin, amoxicillin), cephalosporins, clindamycin, erythromycin, lincomycin.
- Guinea pigs: penicillins (including ampicillin, amoxicillin), cefazolin, clindamycin, erythromycin, lincomycin, dihydrostreptomycin, streptomycin, bacitracin, chlortetracycline, oxytetracycline, tetracycline, tylosin.
- Hamsters: penicillins (including ampicillin, amoxicillin), cephalosporins, clindamycin, erythromycin, lincomycin, vancomycin, dihydrostreptomycin, streptomycin, bacitracin, oral gentamicin, tylosin.

Analgesics

Because small mammals are increasingly considered by their owners to be part of the family unit rather than just possessions, more clients are expecting appropriate pain relief postsurgically, posttrauma, etc., for their pets. Likewise, veterinarians are much more aware and proactive in providing pain management for their patients. Analgesia results in smoother recoveries, a decrease in systemic stress and resultant stress-related diseases (i.e., gastric ulcers), and a more rapid return to normal behavior and function. Pre-emptive analgesia, or the administration of analgesic drugs during premedication, is now the standard when performing painful procedures.

The two main groups of analgesic medications are opiates and nonsteroidal anti-inflammatory drugs (NSAIDs). These can be combined or used alone. Opioids produce both central and peripheral alleviation of pain and have advantages of being efficacious, safe, reversible, and versatile. Of the opioid receptors, the one that has been demonstrated to be extremely important in pain control is the *mu* receptor.

Although opioids provide the most effective analgesia for most types of pain, they can also cause sedation and can be difficult to prescribe for home use. Potent *mu* agonists (i.e., morphine, meperidine, and oxymorphone) can cause respiratory depression in small mammals. Mixed opioid agonist antagonists (i.e., buprenorphine, butorphanol) have fewer side effects and are most commonly used. The effects of opiates on the cardiovascular system are variable, depending on the species. In ferrets and rats, opiates tend to produce hypotension, whereas in rabbits and mice, they are hypertensive. Use of opiates may also result in ileus.

Butorphanol and buprenorphine, both synthetic opiate partial agonists, are, therefore, the most common opiates used in small mammals. They have minimal respiratory effects and do not cause significant CNS depression. Butorphanol acts mostly at *kappa* and *sigma* opioid receptors, whereas buprenorphine acts at *mu* receptors, which may explain its relatively long duration of action. Mammals have more *mu* receptors, hence an advantage to buprenorphine.

Butorphanol (a synthetic opiate partial agonist that is 4-7 times as potent an analgesic as morphine) has a faster onset of action and shorter duration compared to buprenorphine's slower onset of action and longer duration. Some clinicians use both drugs concurrently in exotic animals to provide rapid analgesia (butorphanol) and longer duration (buprenorphine). However, it is probably preferable to give butorphanol (i.e., as a preanesthetic) followed by buprenorphine at least 2-3 hours later. Butorphanol can produce profound sedation in ferrets, so often lower doses are used in this species compared to other small mammals.

Buprenorphine is 30 times more potent than morphine and exhibits many of the same actions as the opiate agonists. Although few adverse effects of this drug have been reported, on rare occasions patients have developed respiratory depression.

Nonsteroidal, Anti inflammatory Drugs

Nonsteroidal, anti inflammatory drugs (NSAIDs) are increasingly being used in small mammals because of the analgesia they provide in response to pain associated with inflammation (i.e., arthritis and dental problems). However, NSAIDs are not considered adequate for treating severe pain and are usually contraindicated in the patient that has received corticosteroids because of the potential for gastrointestinal ulceration or bleeding. Other characteristics of NSAIDs include their antipyrectic actions and many have a long duration of action (i.e., at least 12-24 hours). Although there is little information concerning the safety and appropriate dosages of NSAIDs in these animals (an off label species), these drugs have been reported to cause gastric ulceration in some species. Sucralfate has been shown to protect gastric cells in vitro.

There are two different COX enzymes that have been described in mammals: COX-1 and COX-2. Historically, compounds with activity against COX-1 enzymes were believed to affect the synthesis of prostaglandins important to normal gastrointestinal and renal function, while inhibition of COX-2 enzymes were solely associated with

altering anti-inflammatory activity. However, more recent work suggests that the activity of the enzymes is not that well delineated. COX-2 inhibitors, though, are less likely to induce the negative side effects associated with COX-1 inhibition.

Meloxicam is probably the most commonly used NSAID used in exotic small mammals, and is available in both oral and injectable forms. Its primary action is the inhibition of cyclooxygenase-2, which mediates inflammation. Carprofen is also more selective for COX-2 activity, and is also routinely used to provide analgesia in exotic pet mammals.

There are, however, potential risks associated with the use of NSAIDs. The four most commonly reported clinical signs in domestic animals are vomiting, anorexia, depression, and diarrhea. Less commonly, gastric ulceration, intestinal ulceration, renal failure, hepatic failure, and death may result.

Corticosteroids

Glucocorticosteroids, which have both anti-inflammatory and potential analgesic effects, are still used too commonly in practice. For example, the rabbit is considered to be a very corticosteroid sensitive species. Steroids in rabbits cause two types of adverse reactions: severe immune suppression and liver toxicity.[4] Small, one time doses of a corticosteroid have been reported to have an adverse effect in a rabbit and even topical or ophthalmic doses can cause gastrointestinal ulceration and immunosuppression in this species. There are very few indications for steroids in rabbits, and extreme caution should be observed when steroids are administered[2]

Current Pharmacodynamic Studies

There are relatively few pharmacodynamic studies in exotic companion pets that are relevant to the medications we use or potentially use in practice.[4] Recently Kansas State University conducted studies to evaluate the pharmacokinetics of three drugs that are (or potentially are) used in rabbit medicine: marbofloxacin, meloxicam, and tepoxalin. Results of these studies are currently being evaluated.

Formulary for Small Mammals

The *Exotic Animal Formulary* (2005) and Ferrets, Rabbits, and Rodents: *Clinical Medicine and Surgery* (2004) list the antimicrobial and antifungal agents, antiparasitic agents, chemical restraint/anesthetic/analgesic agents, ophthalmic drugs, and miscellaneous agents used in exotic small mammals.[1,3]

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