Animal Prescriptions in a Human World – Handling Veterinary Prescriptions in the Community-Practice Setting

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Purpose

This article is written to introduce some of the differences between veterinary patients and human patients that can result in drug therapy differences seen in a community-practice pharmacy setting.

Summary

Veterinary prescriptions are becoming more common in the community-practice setting due to a variety of factors, including cost, availability, convenience and legislation changes. However, veterinary patients are not simply small humans with regards to drug use, and this can be seen in dosages that drastically differ from those used in humans, beyond adjustment for size differences. Therefore, it is important for a pharmacist filling these prescriptions to have an understanding of basic differences regarding drug disposition in veterinary patients as well as factors that may influence toxicity and/or adverse effects. This article also reviews commonly used veterinary drug references that a pharmacist can use in the community-practice setting to aid in review of veterinary prescriptions.

Conclusion

Pharmacists should consider species differences that affect drug therapy and consult specialized veterinary references when filling prescriptions for animal patients.

With 65 percent of homes, or 79.7 million, owning at least one pet, it is no surprise that pharmacists are starting to see prescriptions for veterinary patients. In addition, increasing numbers of Americans are starting to think of their pets as members of the family, which is evidenced in the approximately $60 billion being spent on pet care in 2015, with pet health care accounting for a large portion of this. In 2013, sales of prescription and non-prescription medications for dogs and cats totaled approximately $7.6 billion, and this number is expected to increase to over $10 billion by 2018. While these costs pale in comparison to human healthcare costs, most pet owners are paying these expenses directly out of pocket.[1] Pet health insurance is limited, and when it is used, it is often major medical, meaning the owner submits the claim after the fact.

Despite the expenditures for veterinary healthcare, it's not without its challenges. Unlike human medicine, in which one species is being treated, in veterinary medicine, there is a wide variety of species ranging from dogs and cats to cattle to marine animals to captive wildlife. Also, within each species, there are drastic size differences. For example, it is not unusual for a veterinarian in the course of a day to see a two-kilogram Chihuahua followed by a 45-kilogram Bernese Mountain Dog and then treat a cat, rabbit and horse. All of these animals have vastly different metabolic and toxicity considerations in addition to their obvious physical differences.

Veterinary medicine also has a unique regulatory framework separate from the regulatory framework of human medicine. The Animal Medicinal Drug Use Clarification Act (AMDUCA) became effective in 1994 and outlines the provisions for extra-label drug use in veterinary patients. Extra-label drug use is defined as any use that is different than the labeled use. To use a drug "on-label" requires that the drug be used in the species for which it is approved, for the indication, by the route, at the dose and for the duration indicated in the labeling. Any use deviation from this is considered extra-label. Since compounded products are not FDA approved, the use of these products is always extra-label. AMDUCA provides provisions for when extra-label drug use is appropriate.[2] For all extra-label drug use, there must be a valid veterinary-client-patient relationship (VCPR). This indicates that the veterinarian has examined the animal recently enough to provide a preliminary diagnosis and has assumed responsibility for treatment and follow-up and that the client is willing to follow the veterinarian's recommendations.[3]

After the requirement of a VCPR is met, the provisions for extra-label use are based on whether the animal being treated is considered a food animal or not. A food animal is any animal that may enter the food chain or an animal whose byproducts, such as milk, eggs or honey, will enter the food chain. For food animals, a withdrawal time must be established whenever a drug is used. This is the time frame from the last dose of medication until the animal can be sent to slaughter or until its byproducts can be used. FDA-approved products for food animals provide a withdrawal time as part of the labeling. However, if extra-label use is employed, this withdrawal time must be extended to prevent any drug residue from entering the human food supply. Therefore, AMDUCA requirements for extra-label drug use are stricter for food animals than for non-food animals.

Since food animal prescriptions are unlikely to be seen in the community-practice setting, the focus going forward will be on non-food animals. For non-food animals, AMDUCA indicates that the first choice for drug therapy should be an FDA-approved product used as labeled. However, AMDUCA does allow for use of the identical human product, and lower cost is an acceptable reason to select a human-approved product over a veterinary one. For example, there is a veterinary approved fluoxetine chewable tablet (Reconcile®) available to treat canine separation anxiety. However, the human-approved fluoxetine is often a more cost-effective option. According to AMDUCA, use of the human fluoxetine product to treat canine separation anxiety is appropriate as an initial choice. If there is not an approved product that can be used according to the label, then extra-label use of an approved product can be considered. This can be extra-label use of a veterinary product or a human product. If there is no approved product that can be used as labeled or in an extra-label manner, then compounding can be considered.[2]

Since extra-label drug use requires a VCPR, using a product in an extra-label fashion requires a prescription. Where this becomes important to a community-practice pharmacist is when using human over-the-counter products to treat veterinary patients. Human over-the-counter products are only labeled for use in people and are therefore considered extra-label whenever used in animals. This means that prescriptions are technically required for all human medications for veterinary use, regardless of whether the medication is available over the counter or not, and pharmacists are not legally allowed to recommend extra-label use of these products for animals. For example, a pharmacist recommending that an owner give his or her dog diphenhydramine to treat allergies without a prescription from a veterinarian would be similar to a pharmacist recommending that a human patient take three or four 200-milligram ibuprofen tablets instead of seeing his or her physician for a prescription for the higher strength. However, a pharmacist could recommend obtaining the correct strength of the flea and tick preventative fipronil (Frontline(R)) for use in a dog per the labeled directions since this is a veterinary-labeled over-the-counter product. While it is true that some veterinarians will advise clients to pick up an over-the-counter medication without a prescription, if a veterinarian writes a prescription for something available over the counter, it was likely done to ensure that the medication would be correct, have appropriate directions affixed to it and be filled as a prescription medication. If a client comes to the pharmacist with questions regarding a veterinarian recommended over-the-counter product, the pharmacist can answer straightforward questions regarding if the product is what the client is looking for. However, if the questions require professional judgment, it would be prudent for the pharmacist to contact the veterinarian regarding the questions. Also, note that while generic and brand-name products are interchangeable with regard to the active drug, inactive ingredients can be problematic for veterinary patients, so the client should be directed to obtain the product recommended by the veterinarian.

Veterinarians are legally allowed to dispense medications in-house. Historically, veterinarians treated their patients without the involvement of a pharmacist by stocking all of the necessary medications in their clinics. Today, veterinarians are still able to obtain human medications in addition to veterinary-labeled products. However, since AMDUCA allows for the use of human-approved medications in place of the veterinary versions, additional regulations have recently been proposed at the federal level and passed at the state level requiring veterinarians to offer or supply prescriptions for medications instead of dispensing in-house. The American Veterinary Medical Association (AVMA) code of ethics states that veterinarians should honor a client's request for an outside prescription whenever the client desires a prescription over having the medication filled at the veterinary clinic.3 In addition, federal legislation has been proposed multiple times that, if passed, would require veterinarians to physically hand a prescription to the client and then allow the client to decide if he or she would prefer to have it filled by the veterinarian or taken to an outside pharmacy. However, multiple states have enacted their own laws regarding providing prescriptions. These regulations vary by state, with some states requiring a prescription be provided if the owner asks for one and others requiring the veterinarian to offer one every time a medication is needed. Regardless of whether a federal law is passed, whether your state requires a prescription to be offered, or whether the veterinarians are following AVMA's ethical guidelines on providing a prescription, more veterinary prescriptions are ending up in community pharmacies due to the increased availability of rarely used human medications, decreased cost or both. Pharmacists are the only healthcare providers legally allowed to provide care for both human and animal patients. While the exact wording in pharmacy law varies by state, pharmacists are generally expected to be able to evaluate and provide counseling on prescriptions regardless of whether the prescription is for a human or an animal.

When treating animals, it is important to take into account the differences between species with regard to anatomy and physiology. Most animals are horizontally oriented, which decreases the effect gravity has of moving orally administered dosage forms through the esophagus. The end result is that tablets and capsules are more likely to lodge in the esophagus and cause irritation or erosion. While this is a possibility with any medication, doxycycline tablets and clindamycin capsules are the most notorious for causing problems.[4][5] Another species-specific consideration is the cephalic orientation of the breed. Some dogs, such as Labradors and German shepherds, have long snouts, while others, such as pugs and bulldogs, have squished faces resulting in a more restricted upper respiratory tract. These squished-faced breeds are known as brachycephalic breeds and can be more susceptible to the respiratory adverse effects of drugs.[6] It is also important to note that dogs are unable to sweat and instead rely on panting to cool themselves. When drugs that may cause respiratory depression are administered, it is important that the dog not be left out in the heat for long durations because its cooling mechanism is likely to be affected.

The traditional diet of the species being treated can affect drug absorption and elimination. Dogs and cats are carnivores and, therefore, have a more acidic gastrointestinal (GI) tract than humans.[7] The GI tract is also shorter and faster to aid in elimination of the nitrates and nitrites produced by digestion of a meat-heavy diet and to kill bacteria that may be ingested with a raw-meat diet.[8] This has a couple of implications on drug therapy. First, the more acidic environment can lead to increased ionization of basic drugs and decreased ionization of acidic drugs. Unionized drugs are more likely to be absorbed than ionized drugs. The urinary pH is also more acidic in dogs and cats than in humans. Based on the same ionization principles, this can lead to increased and decreased tubular reabsorption of drugs.[9] Enteric coated dosage forms designed for humans may not be as effective in dogs because they are often designed to degrade in more basic pH environments, which may not be encountered in the dog. Also, extended-release products that are designed to elute drug over an extended period may not have time to release the full dose before they are eliminated. Other species have GI tracts adapted to herbivorous diets. For example, rabbits and horses are hind-gut fermenters, which means that they have bacteria colonization in their ceca to facilitate digestion of plant matter. Certain antibiotics, such as clindamycin, can destroy this normal flora to the extent that death can result from endotoxemia due to gram-negative bacteria overgrowth.[10] These factors as well as others can drastically affect the necessary dosage of medications beyond dosage modification for weight.

Animals differ greatly from humans and within the same species regarding drug bioavailability, metabolism and elimination. For example, cats are limited in the ability to perform glucuronidation. In humans, one of the major elimination pathways for acetaminophen to avoid production of the toxic metabolite NAPQI is glucuronidation. Since cats are unable to glucuronidate, acetaminophen is metabolized to the NAPQI, which can lead to cell atrophy and accumulation of reactive oxygen species leading to methemoglobinemia, Heinz body formation and hemolytic anemia. An acetaminophen dose appropriate for a small child can kill a cat within a matter of hours.[11][12][13] Cats are also limited in their ability to perform glycine conjugation. This is important with regard to the metabolism of aspirin. In humans, aspirin is primarily eliminated

as salicyluric acid, which is the product of glycine conjugation, with glucuronidation making up the remainder of the metabolism. However, with cats being deficient in both of these pathways, the half-life of aspirin is approximately 22 hours in cats versus two hours in people. Aspirin is not contraindicated in cats but requires a much different dosing interval of a very small dose every third day. Dogs, on the other hand, are deficient in the ability to acetylate. This is significant when considering the use of procainamide. The active metabolite of procainamide, NAPA, is considered responsible for a large portion of the action of this drug. However, formation of NAPA requires acetylation, which occurs much more minimally in dogs than in humans.[12] This drug could still be an appropriate option, but the decreased NAPA formulation must be taken into account.

In addition to differences between species, there are also differences within species. For example, Japanese strains of beagles have shown different pharmacokinetics for some medications compared to other beagle strains.14 One of the most notable intraspecies variations occurs in dogs with the ABCB1 (MDR1) mutation. This mutation results in an inactive PgP pump. When there are functioning alleles of this gene present, the PgP pump prevents certain drugs from crossing the blood-brain barrier and entering the Central Nervous System (CNS). However, certain breeds of dogs, such as collies and Australian shepherds, are likely to have a mutation to this gene, causing lack of function of the PgP pump. The result is that certain drugs, such as fluoxetine, ivermectin, ketoconazole and cyclosporine, among others, are more likely to cause CNS toxicity, especially at the higher end of the dosing range. Ivermectin is the active ingredient in the common heartworm preventative Heartgard(R). However, when used at these dosages, it does not pose a problem for dogs with the mutation. Problems occur when the drug is used off-label at higher dosages.[15][16]

Some inactive ingredients present in human medications may be toxic to certain species. For example, xylitol, which is a sweetening agent that is often found in liquid medications, is not absorbed by humans and most other species. However, dogs absorb xylitol, which can lead to hypoglycemia and hepatotoxicity.[17] The most common medication of concern is gabapentin liquid. Most of the FDA-approved gabapentin liquids contain xylitol, making it imperative that specific brands without xylitol be dispensed or that a product be compounded when gabapentin liquid is used in dogs. In cats, benzoic acid derivatives, which are often used as preservatives, must be conjugated with glucuronide or glycine, both of which are deficient in cats, potentially leading to methemoglobinemia, especially if used long term. However, small amounts are OK, such as in metronidazole benzoate compounds.[18] Cats are also intolerant of propylene glycol, which can lead to Heinz body anemias. Injectable medications approved for use in humans can contain high percentages of propylene glycol, which can be problematic in cats.[19]

Bioequivalence is another consideration when using human-labeled products in animals. The studies that are done to determine bioequivalence between brands and award drugs an AB rating, are done in humans and do not necessarily translate to animals because different excipients can affect absorption. Many generic drugs are used interchangeably without concern for brand; however, certain drugs, such as itraconazole, have been shown to produce different levels of efficacy between brands.[20] If a veterinarian specifies a certain brand of a medication, it is important to contact the veterinarian prior to switching brands due to risk of different efficacy in veterinary patients, even if the medications are bioequivalent in humans.

The above information touches on some of the differences between dogs, cats and humans. However, a complete discussion of differences is beyond the scope of this article. To aid the community-practice pharmacist in evaluating the appropriateness of veterinary prescriptions in light of the various metabolic and anatomical differences, there are a number of drug references available that specifically address dosing recommendations and adverse effects for veterinary patients. One reference is Plumb's Veterinary Drug Handbook, which is written by a PharmD and is available in hard-copy, online-database and app formats. The book consists of drug monographs that cover indications, dosing, pharmacokinetics/pharmacodynamics, adverse effects, contraindications/precautions, client counseling points and available dosage forms. The app and website are similar in design to the common human drug databases and also contain links to detailed client handouts. Another reference is Saunders Handbook of Veterinary Drugs, which is written by a veterinarian who is board certified in veterinary pharmacology. This book features common indications and dosages as well as adverse effects. There is also a companion website that has free client handouts for a number of medications.

The Merck Veterinary Manual is available free online at **http://www.merckvetmanual.com/** and contains overviews of common disease states and treatment options. It also includes illustrations that can be beneficial from a teaching perspective.

The Companion Animal Parasite Council (CAPC) website is another free online source. It's available at **https://www.capcvet.org/** and provides parasite prevalence maps and recommended treatments for various parasitic infections.

DailyMed, which is a free website available at **https://dailymed.nlm.nih.gov/dailymed/**, provides package inserts for both human and veterinary-labeled drugs.

Finally, the veterinarian prescribing the medication is an invaluable resource. Veterinarians are generally happy to answer questions from a pharmacist trying to do his or her due diligence when reviewing a prescription and would much rather receive a phone call to verify something than have the pharmacist guess wrong, leading to ineffective therapy or patient harm. There are a number of reports of errors occurring that cause patient harm, and these are often the result of the pharmacist altering the dosage or prescription based on what would be appropriate for a human.[21] When in doubt, the veterinarian is a phone call away.

Once the pharmacist has an appreciation for the differences mentioned above and appropriate references to verify dosing and indications, differences between veterinary and human prescriptions need to be considered. In general, the legal requirements for human prescriptions apply for animal prescriptions, but there are a couple of notable differences that a pharmacist may encounter. First, weight is an important consideration. Weight is not a required field on prescriptions in many states but is a critical piece of information when evaluating a veterinary dose. With the wide range of sizes within each species, drugs are often dosed in milligrams/kilogram, which results in a wide range of what could be appropriate in dogs. For example, tramadol may be dosed at five milligrams/kilogram three times a day. For the two-kilogram Chihuahua mentioned at the beginning, this would result in a dose of 10 milligrams three times a day, but for the 45-kilogram Bernese Mountain Dog, it would be 225 milligrams, or four and a half 50-milligram tablets three times a day.[22] Especially when looking at controlled-substance prescriptions, it becomes important to determine if the amount prescribed is appropriate, which requires knowledge of the weight or at least the breed.

Pharmacists may also notice the abbreviation SID on prescriptions from veterinarians. This abbreviation is short for seminal in die, which is Latin for once in a day. Veterinarians have traditionally used SID to indicate once a day and often are unaware that the human medical profession uses QD. Although it is advisable to write out once a day and avoid abbreviations for this altogether, pharmacists are still likely to see prescriptions with SID. Another difference is the National Prescriber Identification (NPI) number, which is provided to anyone who can legally prescribe for Medicare and Medicaid patients. Since animals are not eligible for Medicare and Medicaid and veterinarians are only allowed to prescribe medications for animal patients, veterinarians are not legally allowed to have NPI numbers.[23] The DEA also urges against using the DEA number for identification purposes for noncontrolled substances, resulting in a license number being the only official identification a veterinarian is able to provide.[24]

Pharmacists are one of the most accessible healthcare professionals and the only ones legally allowed to treat both human and animal patients. Therefore, pharmacists have a corresponding responsibility to make sure that they are prepared for the veterinary prescriptions that are likely to arrive in a community pharmacy. This paper outlines some of the common differences seen with a few select species, and the pharmacist filling veterinary prescriptions is strongly encouraged to consult the above references for the medications they are filling.

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