Five things every community pharmacist should know when dispensing for 4-legged patients

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Introduction

Veterinarians are responsible for the entirety of a companion animal's care, including the dispensing of medications. In recent years, both the Internet and media have significantly influenced pet owners to seek alternative means than the veterinarian to obtain medications by advertising substantial cost savings.¹⁻⁵ The average markup on veterinary prescriptions is 100% to 200% plus a dispensing fee.⁶ As a result, more pet owners are asking veterinarians to write prescriptions. This shift has become so noteworthy that Bill S. 1200, The Fairness to Pet Owners Act, has been introduced to the United States Congress.⁷ This bill would obligate veterinarians to write a prescription for all medications and give pet owners the freedom to "shop around" for the best price on their pet's medication. If this bill is passed in the United States, there is no question that a similar piece of legislation will be considered in Canada.

With an increase in veterinary dispensing, there is a need for pharmacists to continue their professional education in the area of animal health. As of 2015, the only Canadian university with an undergraduate elective course in veterinary pharmacology is the University of Alberta.⁸⁻¹⁷ This implies that the majority of Canadian pharmacists do not receive adequate training to dispense animal prescriptions. More concerning, a survey conducted in Oregon revealed several cases of pharmacists making inappropriate medication substitutions or providing incorrect counselling on veterinary medications without consultation with the prescribing veterinarian.¹⁸ For example, the Latin veterinary abbreviation *sid* (once daily) is often misinterpreted by pharmacists as *qid*, resulting in a 4-fold

overdose of the medication. Unfortunately, many of these described cases resulted in patient harm or death. As a result, the veterinary community is quite concerned with the dispensing of veterinary medications by pharmacists.¹⁹⁻²²

The purpose of this article is to educate Canadian pharmacists on the 5 most common issues they may encounter in community practice with regard to veterinary prescriptions. The information provided is an attempt to prevent veterinary medication errors and reduce harm to our animal patients.

Canine levothyroxine prescriptions

Hypothyroidism is the most common endocrine disorder in dogs, affecting 0.4% of the dog population, usually during middle age (7 years).²³ Levothyroxine prescriptions for canines are quite common and can be a source of confusion for many pharmacists because of high doses when compared with human patients.

There are several reasons why levothyroxine dosages are much higher for canines. First, dogs have higher daily requirements for thyroid hormone than humans, because of their physiology. Dogs secrete approximately 8 µg/kg/d of thyroxine (T_4) from their thyroid gland compared with approximately 80 µg/d (1.2 µg/kg/d) for an average 70 kg human.^{24,25} Second, levothyroxine is more poorly absorbed by canines than humans. Canine oral bioavailability for levothyroxine varies from 10% to 50%.²⁴ Human bioavailability for levothyroxine ranges from 64% to 81%.²⁶ Finally, levothyroxine half-life is much shorter in dogs compared with humans. Half-life can vary between dogs, but the accepted range is approximately 8 to 16

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According to Mahatma Gandhi, "The greatness of a nation and its moral progress can be judged by the way its animals are treated." Pharmacists can contribute to the well-being of animals by providing the same compassion and care as we do to our human patients.

D'après Mahatma Gandhi, « on peut juger de la grandeur d'une nation par la façon dont les animaux y sont traités ». Les pharmaciens peuvent contribuer au bien-être des animaux en leur offrant une compassion et des soins identiques à ceux qu'ils fournissent aux patients humains.

KNOWLEDGE INTO PRACTICE

- More pet owners are filling prescription medications from pharmacies, yet pharmacists have little to no knowledge about dispensing medications to animal owners.
- There have been significant veterinary dispensing errors by pharmacists, causing patient harm.
- The purpose of this review is to educate pharmacists on 5 of the most common veterinary prescription issues that community pharmacists may encounter in practice.
- Pharmacists are perfectly placed in the community setting to help pet owners with medication administration and to collaborate with veterinarians to provide optimal patient care.

hours. In humans, the levothyroxine half-life is much longer, between 144 and 192 hours (6-8 days). Higher per-kilogram daily requirements of T_4 , lower oral bioavailability and short half-life all contribute to higher canine levothyroxine dosage requirements. The initial dose of levothyroxine for canines is 20 µg/kg of body weight twice daily.²⁷ It is not unusual to see levothyroxine prescriptions for up to 800 µg twice daily (recommended maximum dose) depending on the animals' weight. To illustrate, a 16 kg cocker spaniel would require 320 µg twice daily for appropriate thyroid replacement therapy.

Use prednisolone in cats: do not substitute with prednisone

In humans, prednisone is converted to active prednisolone in the liver. Prednisone and prednisolone are considered therapeutically equivalent, and conversion from one form to the other is equivalent on a milligram-to-milligram basis.²⁸ The same cannot be said for cats. In general, cats do not share the same metabolic pathways that humans do, and as a result, many drugs cannot be prescribed because of a lack of metabolic activation of prodrugs or because of a buildup of toxic metabolites.²⁹

For years, veterinarians clinically observed that prednisolone worked much better than prednisone in their feline patients but were lacking scientific data to support this observation.³⁰ In 2005, Graham-Mize et al.³¹ conducted an absolute bioavailability study with 6 healthy cats. Ten milligrams each of oral prednisone, oral prednisolone and intravenous prednisolone were administered with appropriate washout periods. Prednisolone serum levels and other pharmacokinetic parameters (C_{max} ,

T_{max} , AUC) were determined by multiple timed blood samples. The investigators found that oral prednisone had an oral bioavailability of only 21% versus nearly 100% for oral prednisolone.³¹ Similarly, a second study from Center et al.³² revealed an AUC of 5259 ng/mL/h for oral prednisolone and 1454 ng/mL/h for oral prednisone in 5 cats, suggesting an almost 4-fold greater activity for oral prednisolone. Both studies concluded that prednisolone should be the preferred drug in cats because of its higher bioavailability. It is unclear why this is the case; some postulated reasons include lower oral absorption, rapid first-pass elimination of prednisone, varying reversible metabolism from prednisone to prednisolone and vice-versa (recycling), or rapid overall renal elimination.³² From the studies described above and with clinical observation, we can agree that prednisolone should never be substituted with prednisone because of the risk for subtherapeutic glucocorticoid concentrations and therefore potential treatment failure in felines.

Never recommend over-the-counter pain medications for animals

Osteoarthritis, also known as degenerative joint disease, is very common among both cats and dogs, especially during their senior years.²³ A community pharmacist may receive inquiries from pet owners about what over-the-counter (OTC) pain control medications to use for this condition. OTC human analgesics must never be recommended to companion animals outside of a veterinarian's specific recommendation, because of significant safety reasons and severe consequences to an animal's health.

Acetaminophen (Tylenol) is absolutely contraindicated for felines. Cats lack hepatic glucuronidation and sulfation enzymes that are required for appropriate metabolism and excretion of acetaminophen. Alternative metabolic pathways facilitate a buildup of the toxic metabolite N-acetyl-para-benzoquinone imine (NAPQI), with toxic signs and symptoms appearing with as little as 10 mg/kg.^{27,29,33} To put this in perspective, just one-half of a regular-strength acetaminophen tablet (162.5 mg) would deliver 32.5 mg/kg to an average 5 kg house cat, which could potentially be fatal without intervention. Buildup of NAPQI causes blood dyscrasias (anemia, methemoglobinemia), hepatic failure and kidney failure, resulting in death if not recognized and treated promptly.³³ Acetaminophen dosages are

available for dogs but are rarely considered a treatment option for analgesia because of poor metabolism and risk of toxicity compared with humans.²⁷ It is also important to be aware of combination products containing acetaminophen, such as Tramacet (tramadol/acetaminophen). Tramadol alone can safely be used in dogs for pain management or cough suppression, but an error in dispensing a combination product has the potential to be extremely harmful.^{27,33}

For canines, nonsteroidal anti-inflammatory drugs (NSAIDs) are a first-line option for pain relief in many clinical situations, especially for the management of degenerative joint disease. However, veterinarians avoid OTC NSAIDs (e.g., ibuprofen, naproxen) because animals are more sensitive to their side effects.³⁴ The preferred prescription NSAIDs that have long-term safety data in veterinary patients, such as carprofen, and/or high COX-2 selectivity, such as carprofen, meloxicam, deracoxib or firocoxib, reduce the chance for gastrointestinal ulceration/perforation, kidney impairment and platelet inhibition.

The use of NSAIDs in feline patients is very limited for several reasons. Gastrointestinal ulceration, platelet inhibition, and renal failure have been documented as severe adverse events causing fatality.²⁷ High-quality, long-term safety data for chronic NSAID use are sparse in the literature. Lack of glucuronidation pathways in felines precludes the use of many NSAIDs because of poor metabolism and excretion. Interspecies differences exist in the expression of COX enzymes, which makes studying COX selectivity in felines (and dogs for that matter) difficult.^{34,35} The ratio of COX-1 to COX-2 selectivity should be interpreted with caution from each clinical study.³⁴ There is emerging evidence that meloxicam may be safe for long-term use in felines for long-term pain conditions,³⁵⁻³⁷ but the veterinary product monograph for Metacam (meloxicam) oral suspension for cats currently does not advocate for use beyond 5 days of therapy.^{27,38}

Acetylsalicylic acid (ASA) deserves special attention because pharmacokinetics in cats and dosage forms for dogs are quite different from other NSAIDs. ASA is not approved for veterinary use; it is used off-label by recommendation and under the supervision of a veterinarian. Although this is an economical choice for pain management or antiplatelet activity, it comes with a high risk for gastrointestinal adverse effects. ASA has a very long half-life (about

MISE EN PRATIQUE DES CONNAISSANCES

- De plus en plus de personnes se procurent les médicaments d'ordonnance pour leurs animaux dans les pharmacies, mais les pharmaciens possèdent peu, ou pas de connaissances sur le sujet.
- De nombreuses erreurs de délivrance de médicaments destinés aux animaux ont été commises par des pharmaciens, au détriment du patient.
- L'objectif de cet examen vise à présenter aux pharmaciens les cinq problèmes de prescription de médicaments destinés aux animaux les plus courants qu'ils pourraient rencontrer dans leur pratique.
- Les pharmaciens sont en parfaite position dans leur milieu communautaire pour aider les propriétaires d'animaux à administrer les médicaments et pour collaborer avec les vétérinaires afin d'offrir aux patients des soins optimaux.

30 hours) in cats because of their lack of glucuronidation pathways, and therefore, much lower doses are required compared to humans.³⁴ Dogs are more sensitive to ASA's side effects and are at higher risk of gastrointestinal bleeding.^{27,39} Enteric-coated ASA tablets have been shown to accumulate in dogs' stomachs over multiple doses (gastric retention), leading to erratic salicylate absorption in addition to fecal elimination of the tablet without disintegration.^{34,40,41} Buffered ASA (i.e., Aspirin Stomach Guard) contains calcium carbonate as an acid neutralizer and is the recommended dosage form for use in dogs. In summary, pharmacists should never recommend ASA use in companion animals unless the veterinarian has been consulted and is actively monitoring the patient.

Insulin for cats and dogs with diabetes mellitus

Diabetes mellitus in companion animals is not classified as type 1 or type 2 as in humans, but dogs are considered completely insulin dependent, whereas some cats may be able to use oral hypoglycemic medication (sulfonylureas).^{23,42} According to the American Animal Hospital Association Diabetes Management Guidelines for Dogs and Cats, insulin is the mainstay of treatment for both dogs and cats diagnosed with diabetes mellitus.⁴³

In dogs, the most commonly prescribed types of insulin are Caninsulin, human NPH insulin and insulin detemir (Levemir). Caninsulin (Vetsulin in the United States) is a veterinary porcine lente insulin zinc suspension that is a 30/70 mix with 2 peaks following subcutaneous injection.

Thirty percent is amorphous insulin that provides a more acute onset of activity, with a peak at 4 hours, and lasts approximately 8 hours. The other 70% is crystalline insulin that is longer acting, providing a second peak at approximately 11 hours. The total duration of activity can vary between dogs, between 14 and 24 hours, and it can be administered either once or twice daily, depending on blood sugar curve results. It is important to note that Caninsulin is U-40 insulin, meaning it contains 40 U/mL and requires special U-40 syringes to administer. Caninsulin cartridges are available for administration through a veterinary insulin pen (VetPen), but caution should be used in large dog breeds that have thicker skin, in which penetration of the 28-gauge pen needle may be insufficient for subcutaneous administration. Treating large dog breeds with Caninsulin can become very expensive, and therefore, other insulin options are available. Human NPH insulin can also be used in canines, but it should be noted that the duration of action is often less than 12 hours.⁴³ The use of long-acting insulin detemir (Levemir) is on the rise as more evidence becomes available for use in dogs. One study demonstrated little difference in day and nighttime glucose fluctuations between NPH insulin and insulin detemir using continuous glucose monitoring.⁴⁴

In cats, long-acting human basal insulin (Lantus, insulin glargine) is the treatment of choice.⁴³ A clinical study demonstrated the superiority of insulin glargine over protamine zinc and other lente insulins in terms of glycemic control and probability of remission.⁴⁵ Within 3 to 4 months of appropriate dietary changes and initiation of insulin glargine therapy, 80% to 90% of cats experience remission of diabetes, in which discontinuation of insulin therapy is possible.⁴² Because of unique differences in metabolism for felines, insulin glargine is dosed twice daily.⁴⁶ ProZinc (human recombinant protamine zinc, 40 mg/mL) insulin for veterinary use is considered a second-line agent since the rates of remission are less than insulin glargine.^{42,43} Protamine zinc is also more difficult to obtain in Canada and may require compounding due to supply issues.

Pet owners may consult the pharmacist regarding their animal's insulin therapy or to order diabetic supplies. Table 1 provides answers to common questions the community pharmacist may encounter in practice regarding diabetes care in companion animals.

Strategies for administering medications to companion animals

A common issue among pet owners is medication administration. There are several strategies that can be used to assist in administering medications to companion animals.

The most common strategy is to try to hide medications using food. This strategy is usually more successful in dogs than in cats. Cats are more likely to chew their food and may bite down on the hidden medication, whereas dogs tend to "gulp" their food without discrimination.^{49,50} Best results can be achieved if the food is a high-reward treat that is not routinely given. Some owners describe their pets picking out the medication if it is not hidden well inside the treat or meal. Other options include Pill Pockets, which are manufactured soft treats with an intentional pocket for pills,⁵¹ and Pill Paste, a soft, flavoured paste designed to mask the taste of medications.⁵² It is also important to employ behavioural strategies to trick the animal into receiving medication. After several doses, the animal may be conditioned to hide if the owner is preparing the medicated treat. To rectify or prevent this behaviour, the owner should give the same treat at different times (nonmedicated) throughout the treatment period to prevent anticipatory aversion.⁵³

If hiding the medication in food/treats fails, the pet owner can administer the medication directly without the aid of food. Pill poppers or pill "guns" can assist in administering medications in capsule or tablet form. Pill guns are shaped like syringes and hold a pill at the rubber tip. They allow the owner to place a pill over the back of the animal's tongue without risk of being bitten. Once the pill is released, the owner can stroke the animal's neck or blow into the nose sharply to encourage swallowing.^{49,50} This process can also be completed without an administration device if the owner feels confident in restraining the animal and does not fear getting bitten. Liquid medications are given in a pouch between the animals' teeth and cheek. It is important not to squirt liquid medication into the back of the throat of an animal with their head tilted back as this is a risk for aspiration/choking.^{49,50}

Finally, specialty compounding pharmacies can compound pet-friendly dosage forms such as flavoured liquids, medicated treats or transdermal formulations. As a pharmacist, it

TABLE 1 Common questions and answers the community pharmacist may receive about insulin for companion animals^{23,42,43,47,48}

Question	Answer
Q: How do I administer half-units of insulin?	A: Purchase insulin syringes that are calibrated with ½ unit increments. For example, a 3/10 cc insulin syringe for 100 U/mL human insulin has half-unit increments up to 30 units total. Some insulin may be diluted to make measuring easier for pet owners, but this may affect the stability of the product.
Q: I'm giving my pet Caninsulin/ProZinc. Can't I just buy human insulin syringes, since they're cheaper?	A: Caninsulin and ProZinc are both U-40 (40 U/mL) insulins. Special U-40 syringes are calibrated for 40 U/mL insulins. Using a human insulin syringe calibrated for U-100 (100 U/mL) will result in underdosing the animal by a factor of 2.5. Conversion tables are available if the pet owner insists on using U-100 syringes. www.felinediabetes.com/insulin-conversions.htm
Q: How do I administer insulin to my pet?	A: Insulin should be administered subcutaneously by pinching a fold of skin at least 1-2 inches below the spine into a "tent." It is important to rotate sites to prevent formation of fat deposits/fibrotic tissue. The "scruff" of the neck is a less optimal site because it is poorly vascularized and has poorer absorption. There are several how-to websites that show pictures of proper injection technique: www.mypet.com/pdfs/vetsulin/Vetsulin-Canine-Administration-Guide.pdf
Q: What are signs and symptoms of hypoglycemia in a dog/cat?	A: Mild: Lethargy/weakness, head tilting, hunger, restlessness Moderate: Ataxia, confusion/disorientation, vocalization, glassy eyes Severe: Seizures, coma
Q: What should I do if I see symptoms of hypoglycemia in my dog/cat?	A: If mild, offer the animal some food. If moderate symptoms present, dextrose gel, honey or corn syrup can be offered with or without additional food or rubbed on the gums to raise blood sugar. Do not pour the solution into their mouth, as this is a choking hazard. If the animal is unconscious or having a seizure, use your finger to rub corn syrup on the gums and seek veterinary medical attention immediately.
Q: My veterinarian told me to get a glucose meter for my pet. Can I use a human meter or are there meters specifically for pets?	A: Human glucose meters can be used for dogs and cats. They have been used in veterinary medicine for quite some time. If the owner requests a pet-specific meter, there are a few blood glucose meters marketed to pets: the iPet, AlphaTRAK 2 and GlucoPet. Acquiring the pet-specific meter and test strips may be more costly to the owner.

is important to consider flavour preferences of both cats and dogs. Cats prefer fish and chicken flavours and lack a sweet taste receptor due to being obligate carnivores.⁵⁴ Dogs, on the other hand, do have a sweet taste receptor and prefer sweet and/or meaty flavours such as peanut butter, beef, pork and lamb.^{55,56} It is important to note that the majority of medications compounded for animals do not have established safety and efficacy studies compared with commercial dosage forms meeting good manufacturing practices. Therefore, specialty compounding should be considered only when all other treatment options including human and veterinary dosage forms and administration techniques have failed.⁵⁷⁻⁵⁹

Conclusion

This article highlights yet another example of specialized services a pharmacist can provide to a unique patient population. Differences in both physiology and pharmacokinetics play an important role in companion animal prescribing. To ensure the safety of our animal patients, maintaining an open line of communication with the veterinarian is paramount. With the benefits of the human-animal bond well documented in the literature, extending beyond simple companionship,^{60,61} we must consider the health of companion animals as part of our professional education. After all, pets are patients too, and we should offer them the same exemplary care we do to their 2-legged friends. ■

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