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Compounding: Goal remains to fulfill unmet need

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Q. Please review concepts of compounded drugs for cats and dogs.

A. Dr. Mark G. Papich at the 2005 American College of Veterinary Medical Internal Medicine Forum (ACVIM) in Baltimore gave a lecture on the safety and efficacy of compounded drugs. Some relevant points in this lecture are provided below.

Historically, veterinarians have been known for preparing concoctions, mixtures and remedies for their patients because there were few approved veterinary formulations on the market. Now, however, there are more available drugs for use in animals, and scientists have acquired a better understanding of factors influencing the risks of drug instability as well as the incompatibility of certain mixtures. Concerns regarding the widespread practice of product compounding have been raised with respect to drug stability, purity and potency.

Compounding is the alteration of the original drug dosage form for the purposes of ease of administration or because the original dosage form is unsuitable for the purpose intended. According to the United States Pharmacopeia, compounding involves the preparation, mixing, assembling, packaging and labeling of a drug or device in accordance with a licensed practitioner's prescription. From the USP chapter on pharmacy compounding, "compounding is an integral part of pharmacy practice and is essential to the provision of health care".

Compounding does not include the preparation of a dosage form by reconstitution or mixing if conducted in accordance with FDA-approved manufacturer's instructions on an approved human or veterinary product label.

Case by case

The FDA permits compounding on a case-by-case basis and on the order of a veterinarian when there is a need for an appropriate size oral dosage form to produce a more palatable oral drug, to produce a more dilute formulation for a small animal or exotic animal patient, or when it is necessary to admix anesthetics for ease of administration. These are expected practices and will not be subject to regulatory action.

"Bulk drugs" are defined as active ingredients used in the manufacture of finished dosage forms. Compounding from bulk drugs or from unapproved drug substances is not allowed, but there are a few chemicals for which some compounding from bulk drugs will not ordinarily be subject to regulatory action. Compounding of these latter compounds is allowed in instances where the health of the animal is at risk and when no other remedies are available. The list includes antidotes such as methylene blue or sodium nitrite.

Palatability, ease of administration and dispensing factors are among the considerations used when formulating drugs for animals. Drugs intended specifically

for animals and registered by the FDA are designed with great care. Pastes and dosage syringes are available for some drugs used in horses. Flavored tablets are often available for dogs to ease administration by pet owners. To prevent parasite infestations, transdermal medications are available for dogs and cats to avoid the necessity of frequent administration to a pet that can be difficult to medicate. One of the largest costs to pharmaceutical companies when developing new drug products is the determination of an appropriate formulation. When companies spend literally millions of dollars getting the formulation right in terms of stability, solubility and palatability, it is risky to expect that new drug formulations compounded in a pharmacy will have the same assurance of stability, purity and potency.

When necessity prevails

Compounding is sometimes a necessity. Despite advances in new drugs available for animals, many unmet needs still remain. Therefore, many drugs are crossed over from one animal species to another, or are human drugs administered to animals. The top 10 drugs that are compounded for veterinary medicine are potassium bromide, metronidazole suspension, methimazole oral liquid, diethylstilbestrol capsules, cyclosporine ophthalmic solution, prednisone oral liquid, amitriptyline oral liquid, chloramphenicol oral suspension and protamine zinc insulin. Much of the compounding cited in the article consisted of mixing drugs with various foods and flavorings in an effort to ease product administration to hard-to-medicate pets or exotic species.

Some compounded drug formulations can present problems if the safety and potency of the compounded product have not been considered. Tablets that must be crushed or broken to deliver a smaller dose size to dogs or cats may be unpalatable for oral use in animals. When drugs are administered to cats, either a portion of a tablet must be given or the drug is reformulated into a capsule. Because ill cats are usually anorectic and because cats generally do not drink water frequently, solid-dose forms have become trapped in the esophagus of cats. The location of the entrapment of capsules is particularly disturbing because some medications given to cats, such as doxycycline, tetracycline, propranolol, iron supplements and bromide, are known to cause esophageal lesions in cats.

Because many drugs are not in a form that is ideal for the species being treated (e.g., cats, exotic animals, pet birds), the tablets have been crushed, capsules reformulated and solutions altered to make a more convenient and palatable oral-dosage form. However, when protective coatings are disrupted and vehicles are altered, the stability of the product may be compromised. In some instances, the only change is a slight alteration of pH. Improper pH ranks with exposure to elevated temperature as a factor most likely to cause a clinically significant loss of drug. A drug solution or suspension may be stable for days, weeks or even years in its original formulation, but when mixed with another liquid that changes the pH, it degrades in minutes or days.

It is possible that a pH change of only one unit could decrease drug stability by a factor of 10 or greater. Addition of a water-based solution to a product to create a liquid solution or a suspension results in the hydrolysis of certain compounds (e.g., -lactams and esters). Some drugs undergo epimerization (steric rearrangement) when exposed to a pH range higher than what is optimum for the drug (for example this occurs to tetracycline when exposed to a pH higher than 3.0). Other drugs are oxidized, a reaction catalyzed by exposure to a high pH, rendering the drug inactive. Drugs most likely to be subject to oxidation are those with a hydroxyl group bonded to an aromatic ring structure.

Veterinarians and pharmacists are obligated to be cognizant of the potential for interactions and interference with stability. Oxidation is often visible through a color change (e.g., color change to pink or amber). Loss of solubility may be observed through precipitation. Some drugs are prone to hydrolysis from moisture. A rule-of-thumb for veterinarians is that if a drug is packaged in blister packs or in moisture-proof barrier, it is probably subject to loss of stability and potency if mixed with aqueous vehicles.

If compounded formulations of solid-dose forms show cracking, "caking" or swelling, the formulation has probably acquired moisture and may have lost potency. Another rule-of-thumb is that if the original packaging of a drug is in a light-protected or amber container, it is probably prone to inactivation by light. Vitamins, cardiovascular drugs

and phenothiazines are labile to oxidation from light during compounding. Also, as a general rule, if an antibiotic is available in a powder that must be reconstituted in a vial or in an oral dispensing bottle prior to administration, it should not be mixed with other drugs.

In a commercial formulation, the active ingredients and the excipients added to drug formulations are tested and must meet FDA-approved specifications to ensure the stability of the drug and to ensure uniformity in product in vivo performance. However, the addition of other chemicals, flavorings and vehicles, or compromising the protective coatings of tablets may interfere with the stability of the drug, decreasing its potency, compromise its oral absorption and consequently reduce its efficacy. There are published recipes in compounding journals, magazines and handbooks, but few of these formulations have been tested for their stability, potency and purity.

Veterinarians have an obligation to question their compounding pharmacist about the stability and potency of formulations he/she prepares for their patients and to insist on some valid documentation. When veterinarians compound formulations in their own practices, they should be cognizant of potential interactions that may compromise product performance.

Well-documented problems

For some drugs, the problems with compounding are well-known. Fluoroquinolone antibiotics are frequently modified for administration to exotic animals and horses. This class of drugs is compatible with most mixtures and remarkably stable. A notable exception is the chelation of fluoroquinolones with aluminum-containing products (e.g., antacids, sucralfate), resulting in a significant portion of the medication becoming unavailable for absorption. If crushed orbifloxacin tablets are mixed with a vitamin and mineral supplement that is sometimes used as a flavored vehicle for oral drug administration, potency is reduced to half that seen with the original formulation. The decrease in potency is attributed to the high levels of iron contained within this flavorant. Other flavorings and vehicles (for example, corn syrup, molasses, fish sauce, and Syrpalta (thick grape syrup) had no affect on orbifloxacin stability.

Antifungal drugs also are subject to instability. Itraconazole is frequently compounded from bulk drugs or the proprietary capsules. However, during compounding, inactivation may occur. Itraconazole may adsorb to plastic and glassware, decreasing product drug concentrations — the concentrations of itraconazole are either one-half of the intended potency or undetectable from the compounded capsule. Powdered bulk itraconazole is practically insoluble in aqueous solutions and has poor solubility when administered orally.

Aminoglycoside antibiotics (gentamicin, tobramycin and kanamycin) are inactivated when admixed with other antibiotics, particularly beta-lactams. This interaction is greatest with carbenicillin, followed by ticarcillin, penicillin G and ampicillin. Loss of potency by as much as 50 percent can occur within four to six hours. This interaction is a potential problem when antibiotic mixtures are prepared and dispensed for use several hours later. This interaction does not occur at therapeutic concentrations within the patient because the drugs are diluted in plasma and body fluids.

Drugs formulated as acids — such as the hydrochloride form of basic drugs — are designed to maintain their solubility in aqueous solutions. However, when these formulations are mixed with drugs that are basic, or are added to basic vehicles, drug precipitation may occur.

Several drugs are not soluble in aqueous vehicles. Therefore, they are dissolved in organic solvents (propylene or ethylene glycol) or alcohols. These are notoriously unpalatable to some animals, particularly cats. However, if these formulations are diluted in aqueous fluids, or aqueous flavorings added, precipitation may occur. When these are stored at home by the pet owner, precipitation of the drug to the bottom of the container results in the dosing of a dilute mixture when the container is sampled from the top and a highly concentrated mixture when the container is sampled from the bottom (assuming that the precipitate at the bottom can be re-suspended). This may be observed when mixing some drugs in aqueous fluids. For example if diazepam solution (which contains propylene glycol and alcohols) is diluted in saline solution or lactated Ringer's solution, precipitation occurs.

In some animals, transdermal delivery is ideal because it is convenient and bypasses the intestinal and hepatic first-pass effects. The medications most-often formulated for transdermal delivery to animals are antiparasitic drugs for cattle and anti-flea drugs for dogs and cats. Transdermal applications of human drugs also are used. One such delivery device consists of a patch containing a reservoir of fentanyl that is absorbed through the skin.

Unless the drug is highly lipophilic and formulated in a vehicle that has been shown to enhance transdermal penetration, it is difficult to attain systemic concentrations from transdermally-applied drugs. There have been several attempts by compounding pharmacies to formulate transdermal medications from existing forms of antibiotics, cardiovascular drugs, antithyroid drugs, analgesics, corticosteroids and antidepressants. Bulk drugs also have been used for transdermal compounding. Drugs have been combined with penetration enhancers to facilitate transdermal absorption. One popular example of a penetration enhancer is pluronic lecithin organogel (PLO), which is lecithin that is mixed with isopropyl palmitate and a poloxamer (pluronic).

The ingredients in PLO act as surfactants, emulsifiers and solubilizing agents. Although the use of PLO is popular among the veterinary compounding pharmacies, there are no successful commercial formulations that have combined PLO with systemic drugs. Drugs that have been applied to cats in a PLO vehicle include fluoxetine, glipizide, amitriptyline, methimazole, fentanyl, morphine, dexamethasone, diltiazem and buspirone.

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