Avoiding drug residues in cattle – clearance time considerations in sick cows

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Abstract

Prevention of drug residues in the beef and dairy industries is a major concern as both meat and milk from cattle are widely consumed by humans around the world. This paper will address the keys to avoiding residues; however, there are several things that can change the half-life of a drug and thus affect the withdrawal time. These factors can include route of drug administration, volume administered at each injection site, drug formulation, and disease. The focus of this presentation will be to discuss what is known about disease-induced alterations in the pharmacokinetics of drugs and how clearance time in many cases may be delayed resulting in residue violations. Withdrawal times are generally based on pharmacokinetic studies done in healthy animals; however, there is strong evidence that these times may not always be appropriate in cows with clinical disease. Since pharmaceutical companies must conduct trials to demonstrate the efficacy of various drugs for treating a specific disease or condition during the approval process, it seems logical that pharmacokinetic and residue studies could be done using the same animals or under similar conditions.

Key words: cattle, residues, withdrawal time

Résumé

Prévention des résidus de médicaments dans le secteur de l'élevage des bovins est une préoccupation majeure comme le lait et la viande provenant de bovins sont largement consommés par les êtres humains partout dans le monde. Ce document abordera les touches pour éviter les résidus; toutefois, il y a plusieurs choses qui peuvent changer la demi-vie d'un médicament et, par conséquent, affecter les délais de retrait. Ces facteurs peuvent inclure la voie d'administration de la drogue, le volume administré à chaque site d'injection, la formulation des médicaments, et la maladie. L'objectif de cette présentation sera de discuter de ce qui est connu sur les altérations induites par la maladie dans la pharmacocinétique des médicaments et comment le temps de clairance dans de nombreux cas peut être retardé en résidus résultant de violations. Les périodes de retrait sont généralement fondées sur les études pharmacocinétiques effectuées chez les animaux en bonne santé; toutefois, il existe de fortes preuves que ces délais peuvent ne pas toujours être appropriée dans des vaches avec la maladie clinique. Étant donné que les sociétés pharmaceutiques doivent conduire des essais cliniques pour démontrer l'efficacité de divers médicaments pour traiter une maladie ou un état spécifique au cours du processus d'approbation, il semble logique que la pharmacocinétique et les études de résidus pourrait être fait en utilisant les mêmes animaux ou dans des conditions similaires.

Minimizing Residues in Meat and Milk

Some of the major reasons for residues in cattle include: 1) not following the directions for correct treatment or dose of drug to be administered; 2) failure to follow the appropriate meat withdrawal period after treating cattle; 3) treatment of the animal not recorded on a written record; 4) poor or improper animal identification; 5) extralabel or illegal drug use (using a drug not approved for the animal being treated); or 6) administering a drug in a different way than indicated on the label. Given the frequent use of therapeutic drugs on cattle operations and the potential involvement of farm workers in administering these drugs, veterinarians should be encouraged to set up written protocols for their herds to minimize variability in therapy and inappropriate drug selection or dosing. Unfortunately this is not commonly done in the industry. A survey done in Washington state indicated that only about 25% of farms had written protocols in place for treating common diseases.[18] This is similar to a survey in Pennsylvania where 21% of farms had defined treatment protocols and only 32% of producers sought veterinary advice prior to treating sick cattle.[20] In addition, only about 50% of farms kept any type of written record of antimicrobial use on the farm. Another study found that the lack of adequate treatment records was the most commonly identified reason for residues in New York State.[21] Other major reasons were failure in the understanding of how to properly use drugs by farm personnel and a poor relationship between veterinarians and producers.

In addition, milk residue violations are frequently associated with the following: 1) accidentally milking a treated cow into the bulk tank; 2) milking a cow that has received a dry-cow antibiotic formulation into the bulk tank; 3) pipeline not diverted from bulk tank when milking cows treated with antibiotics; 4) milk put in tank before the appropriate withdrawal period has ended; and 5) extralabel treatment (milk put into bulk tank without an appropriate withdrawal period). Farms with high somatic cell count levels have been reported to have a much higher rate of antibiotic residue

violations, and larger dairy farms have also been shown to have higher rates of residues.[23] In the United States, there are Milk and Beef Quality Assurance Programs which identify critical control points for residue prevention. The programs are designed to be used by cattle producers and their veterinarian as training on how to avoid drug residues. These are voluntary programs in the United States; however, once a farm has a residue violation, they may be required to complete the program in order to regain their ability to sell milk. The critical control points outlined in the program are as follows.

Practice healthy herd management

In this part of the training, the veterinarian evaluates the housing, sanitation, nutrition and reproductive programs, biosecurity, and newborn calf care already present on the farm. Since disease prevention is often more cost-effective than disease treatment, step 1 is designed to help the veterinarian and producer review things like milking management, hoof care, and vaccination programs. Through the process of completing an evaluation of the current herd health management program, ways to improve herd management and reduce the actual number of disease treatments may be identified.

Establishing a valid veterinarian-client-patient relationship (VCPR)

Having a valid relationship between the veterinarian and producer is always helpful when drugs are being used, and is mandatory in many countries if drugs are used in an extralabel manner. A standard definition of a VCPR is as follows:

The veterinarian has assumed the responsibility for making clinical judgments regarding the health of the animal(s) and need for medical treatment, and the client (owner or other caretaker) has agreed to follow the instructions of the veterinarian

There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s) and/or by medically appropriate and timely visits to the premises where the animals(s) are kept.

The veterinarian is readily available or has arranged for emergency coverage or follow-up in case of adverse reactions or failure of the regimen of therapy.

Another part of this portion of the training is to help producers understand the difference between over-the-counter drugs, approved prescription drugs, and extralabel drug use. Producers should have labels on all of their drugs stating the name of the drug, directions for use, prescribed withholding interval, and any cautionary statements. Part of the veterinarian's job is to educate producers on which drugs can be legally used in cattle and which drugs are inappropriate. All drugs on the farm should have labels stating the name of the drug, directions for use, prescribed withholding interval, and any cautionary statements.

Use only approved drugs with veterinarian's guidance

The veterinarian thoroughly reviews the list of prohibited drugs with the producer to ensure that these are never being used on the farm. For example – drugs prohibited for use in the United States include diethylstilbestrol, chloramphenicol, nitroimidazole (including metronidazole), sulfonamides (in adult dairy cattle, with the exception of sulfadimethoxine which is approved), nitrofurans (including topical use), clenbuterol, dipyrone, phenylbutazone, fluoroquinolones (with the exception of approved drugs and indications), and glycopeptides (such as vanomycin).

Maintain milk quality

This part of the training reviews the farm's milking procedures, waste management, and sanitary conditions. Since it is difficult or impossible to improve the quality of milk in the processing plant or retail locations, quality is generally determined at the dairy. The veterinarian reviews cow cleanliness, milking procedures, milk cooling, and also reviews milk quality reports with the producer, monitoring such things as somatic cell counts and bacteria counts.

Make sure all employees are adequately trained

Since there are often many different drugs present on a farm and there are many different routes of administration for drugs in cattle, it is critical that all employees be trained on how to administer drugs properly. Making sure only approved employees have access to drugs and making sure they know how to follow treatment protocols and how to maintain treatment records is vital to avoiding residue violations. As farms continue to get larger, more and more employees are involved in treating sick cattle. Both the veterinarian and the herd manager must ensure all employees have a good understanding of proper drug administration.

Administer all drugs properly and identify all treated animals

There are several routes of administration commonly used to administer drugs to cattle including oral, topical, subcutaneous, intramuscular, intravenous, intramammary, and intrauterine. The veterinarian should review each of these with the producer and make sure they understand how to give drugs via each route. The veterinarian also makes sure the farm is somehow identifying animals when they are treated, such as using leg bands, neck bands, or colored marks. In the beef industry, it is important to make sure all shots are administered in the cervical (neck) region and not in the muscles that represent higher quality cuts (steaks or roast). It is also important to use subcutaneous administration when allowed by label instead of intramuscular.

Maintain and use proper treatment records on all treated animals

The Food and Drug Administration in the United States requires that producers maintain drug treatment records for 2 years on all animals. These records should be easily accessible by anyone who works with the animals. The producer should be able to show where all drug purchases were either used or disposed. The treatment record should contain the date of treatment, drug used, animal identification, dosage, route of administration, individual who administered the drug, and withdrawal period for meat and milk.

Use of drug screening tests

There are various "on-farm" screening tests that are available for use by producers to screen milk for antibiotics. Examples of these rapid assays include Beta Star Plus,[a] Delvotest,[b] SNAP antibiotic residue test,[c] and various Charm II assays.[d] Proper use of drug screening assays, particularly when a drug has been used in an extralabel manner, is strongly encouraged. In this step of the program, a veterinarian reviews how producers identify withholding intervals and assesses whether or not they are correctly using drug screening tests in certain situations. Appropriate use of milk residue test kits on farms has been associated with a significant reduction in the risk of milk residue violations.[14]

Implement employee/family awareness of proper drug use to avoid marketing adulterated dairy products

Many residues result when 1 person treats the animal and someone else does the milking. In addition to maintaining accurate drug treatment records, it is important the all farm employees understand the importance and cost of drug residues and how to avoid them. The use of part-time labor to milk cows was found to be 1 of the most significant risk factors on dairy farms with a high risk of milk residue violations.[14] Therefore all employees should understand how to read drug labels, how to fill in drug treatment records, and how to identify treated cattle.

Complete the milk and beef residue prevention protocol annually

To truly minimize residues, the training discussed above should be reviewed on a yearly basis to ensure everyone on the farm understands how to use drugs appropriately on the dairy farm. Overall the most effective ways to minimize drug residues is through education between the veterinarian and farm manager, and between the manager and farm employees. Establishing a valid relationship between producer and veterinarian should be the first goal, whereby the veterinarian visits the farm regularly, has a thorough knowledge of the diseases and organisms that occur most commonly on the dairy, and establishes written treatment protocols for various diseases that may occur. The veterinarian should also educate the manager and all farm employees on proper drug storage, drug labeling, how to properly administer drugs, identification of treated animals, how to maintain and understand treatment records, and how to establish both meat and milk withdrawal times. Also the proper use of "on-farm" antibiotic screening assays can help reduce the risk of drug residues.

The Effects of Disease on Drug Clearance

In general, drug residues in cattle can be attributed to: 1) failure to adhere to the recommended withdrawal times, 2) poor record keeping, 3) inadvertently administering the wrong drug, dose or dosing via an unapproved route of administration, 4) extra-label drug use without an appropriate withdrawal interval or 5) altered clearance of drugs in diseased animals.[9] Examples of extended withdrawal times when drugs are given by unapproved routes of administration include ceftiofur crystalline free acid (13-day slaughter withdrawal when given in the ear – but can result in residues for up to 90 days when given intramuscularly or 130 days when given subcutaneously somewhere other than the ear. Our laboratory has also shown that the pharmacokinetics and clearance of flunixin was significantly slower when given by the IM or SC routes as compared the approved IV route.[7]

The main goal of drug use in veterinary medicine is to treat diseased animals. Food and Drug Administration guidelines state that that meat withdrawal times be determined using residue data from the target tissue of 20 animals, with 5 animals being slaughtered at each of 4 evenly distributed time points. For milk withdrawal times, 20 animals are used with milk collected from all animals at evenly spaced time points. However, it is not required that animals used in these residue studies have the clinical disease for which the drug is being approved, and healthy animals are generally utilized in these studies. These studies provide the basis for the development of dosage regimens and determination of a withdrawal time, assuming no changes in the dose-effect relationship and pharmacokinetics in diseased animals. This implies that the pharmacokinetic behavior of a drug remains the same in diseased and healthy animals. However, diseased states can profoundly alter the pharmacokinetic behavior of a drug. The most profound differences in pharmacokinetic responses are generally associated with hepatic, renal, and cardiovascular disease, but other processes such as inflammation, endotoxemia, and stress can also significantly alter a drug's absorption, distribution, metabolism, and elimination.[13] In ruminants much of the literature has focused on describing the effect of disease on the pharmacokinetics of various antimicrobials. For example, differences in pharmacokinetics were noted between febrile and afebrile goats administered norfloxacin. The clearance was significantly reduced in 28 febrile goats compared to afebrile goats.[6] Similarly, a 47% reduction in enrofloxacin clearance was observed in febrile goats following an intravenous injection of endotoxin.[17] There was a reduction from 28.8% to 8.5% in the metabolic conversion of enrofloxacin to ciprofloxacin in febrile goats; which is likely responsible for the reduced clearance. As a

result of the reduction in clearance; the elimination half-life and mean residence time were prolonged.[17] In another study where febrile goats were administered marbofloxacin, both the volume of distribution and clearance were significantly reduced compared to healthy animals. Consequently, mean residence time was significantly greater in febrile goats.[24]

A study conducted by Lucas et al found that mammary health status had an influence on the pharmacokinetics of azithromycin.[12] Quarters with subclinical mastitis caused by *Staphylococcus aureus* had significantly lower drug clearance from the mammary gland, a greater milk elimination half-life, and longer mean residence time in milk for azithromycin. Differences in drug pharmacokinetics have also been described for oxytetracycline in cows with theileriosis.[10] Following intramuscular administration, infected cattle had significantly prolonged absorption, elimination half-life, mean residence time, area under the curve, and bioavailability as compared to oxytetracycline administration in healthy cows. Another example is theophylline where in a field trial, 5 out of 20 calves with respiratory disease died after administration whereas all 20 calves treated with a placebo survived.[15] A subsequent study showed calves with pneumonia had significantly higher plasma concentrations of theophylline as compared to healthy calves.[16] Likewise, a greater secretion of ceftriaxone into milk was also noted in cows with metritis as compared to control cows following intravenous administration.[1]

Differences in pharmacokinetics and milk elimination of drugs have also been observed for intramammmary preparations used to treat mastitis. Mastitis produces physical and chemical changes both in the milk and the mammary gland itself that have the potential to alter distribution and elimination of drugs through the mammary gland.[3] Inflammation of the mammary gland leads to vascular permeability changes that often enhance systemic absorption and perhaps distribution of drugs into the udder. For example, gentamicin is not detected in the plasma following intramammary administration in normal quarters; however, the drug is well absorbed in cows with mastitis.[22] Similarly in studies using polymyxin B, the drug was not found in the blood or untreated quarters following intramammary administration in normal cattle; however, significant systemic absorption was seen in cows with experimentally induced coliform mastitis.[25] Lastly, a study using an intramammary preparation of cefoperazone sodium reported significantly greater systemic drug absorption, milk half life, and mean residence time in cows with subclinical mastitis compared to healthy controls.[26]

A more recent study showed that in in cows with clinical mastitis, the clearance of flunixin was significantly slower than seen in healthy cows, and residues persisted beyond the approved withdrawal time even following proper administration of the drug.[8] To go along with this, a recent surveillance study found that cows culled because of disease or that had evidence of disease at slaughter had a significantly higher incidence of violative tissue flunixin concentrations than did healthy dairy cows.[2] Since 2005, the USDA Food Safety Inspection Service has reported an increasing number of flunixin residue violations in meat from dairy cattle. This increase in the number of violations attributable to flunixin residues has led to flunixin becoming the second most common residue violation (behind only penicillin) in cull dairy cattle. Although the reason for the high number of flunixin residue violations isn't well understood, this is a direct example of where disease-induced alterations in drug clearance could be causing delayed clearance and prolonged residues. Or stated simply, the withdrawal time for flunixin established in healthy cattle may not be appropriate following administration in cows with clinical mastitis, which is one of the indications the drug is approved for. Although more work needs to be done, there is clear evidence that health status may alter drug pharmacokinetics and in part be responsible for the high number of residue violations seen in cull cows.[2] Animals in which a disease process has altered either distribution or clearance deserve increased attention to ensure complete drug withdrawal.[13,19] Since pharmaceutical companies must conduct trials to demonstrate the efficacy of various drugs for treating a specific disease or condition during the approval process, it seems logical that pharmacokinetic and residue studies could be done using the same animals or under similar conditions.

As we move into the future, farms are becoming larger in size. This means larger numbers of cows on 1 facility and a greater number of employees involved in the cattle industry. We also have newer and more sensitive analytical methods that are capable of rapidly detecting even small concentrations of drugs that might be present in meat or milk samples. Globally, we are seeing a larger and larger number of milk samples tested for residues every year, which is a trend expected to continue as technology improves. So scrutiny of meat and milk is at an all-time high, which is expected to further increase in the future. All employees involved in the cattle industry should be reminded that drug residues are a significant public health concern, and the meat and milk products get a negative image when reports of drug residue violations become public. It is in the best financial interest of both veterinarians and livestock producers to take positive steps towards reducing and eliminating meat and milk residues.

Endnotes

[a]Neogen, Lansing, MI
[b]DSM Food Specialties, The Netherlands
[c]IDEXX Labs, Inc., The Netherlands
[d]CharmSciences, Lawrence, MA

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