CgFARAD™ NEWSLETTER

FALL 2018

In our 16 years of operation, the identification of residue issues has prompted a number of important drug residue studies by both the CgFARAD™ co-directors and other researchers. This edition of the CgFARAD™ newsletter will highlight some of the current research projects underway or proposed which focus on residue depletion and food safety.

METABOLISM OF LEVAMISOLE IN SHEEP TO COMPOUNDS OF HUMAN HEALTH CONCERN

Dr. Trisha Dowling, Co-director, CgFARAD™

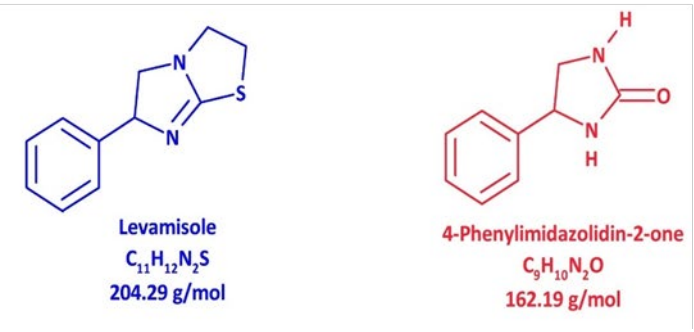
This study was carried out with Dr Fabienne Uehlinger (Large Animal Clinical Sciences, Western College of Veterinary Medicine) and Devan Loganathan (Maxxam Analytics, Burnaby, BC).

In our 16 years of operation, the identification of residue issues has prompted a number of important drug residue studies.

Levamisole is an old anthelmintic for treatment of intestinal parasites in cattle and sheep. Its original approval predated analytical methodology capable of detecting all of its metabolites. Use of levamisole in sheep production decreased with the introduction of safer and more efficacious products, mainly the macrocyclic lactone (ML) drugs. But worldwide resistance to MLs is threatening the viability of sheep production and has renewed interest in the use of levamisole. However, serious concerns have emerged regarding the metabolic fate of levamisole in sheep. Cocaine is commonly adulterated with levamisole and levamisole is rapidly metabolized to aminorex in humans. Aminorex is an amphetamine-like stimulant drug no longer approved for human use due to serious adverse effects. Levamisole-adulterated cocaine is associated with potentially fatal pulmonary hypertension, agranulocytosis and necrotizing vasculitis. The objective of this pilot study was to determine if levamisole administration results in the production of amphetamine-like metabolites in urine and/or blood of sheep.

Three cross bred adult ewes were administered 8 mg/kg of levamisole hydrochloride per os. Urine and plasma samples were collected pre- and at 1, 3 and 6 hr post-dosing. Samples were analyzed at Maxxam Analytics by HPLC-M/MS analysis.

Levamisole and its metabolites 4-phenylimidazolidin-2-one, aminorex and rexamino were detected in post-dosing samples from treated sheep. Sixteen other metabolites were detected in sheep urine but their structures could not be elucidated due to lack of reference standards.



Documentation of amphetamine-like metabolites of levamisole in plasma and urine of levamisole treated sheep indicates that they are likely present in tissues used for human food. The results of this study support further investigation of the metabolic fate of levamisole in sheep and other ruminants and re-evaluation of its approval for use as an anthelmintic.

	Mean Concentration (ng/mL)							
Time	Levamisole		4-Phenylimidazolidin-2-one		Aminorex		Rexamino	
	Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
1	357	3067	80	1067	0.05	6.4	ND	1.1
3	353	7700	77	24,400	0.12	32.3	ND	2.1
6	283	2870	57	1700	0.13	24.3	ND	2.3

MEAT WITHDRAWAL TIMES FOR MELOXICAM USE IN GRAIN-FED VEAL CATTLE

Veal Farmers of Ontario

The Veal Farmers of Ontario (VFO) has applied for funding through the Canadian Agricultural Partnership (CAP) program to complete a meloxicam depletion study on dairy calves for grain-fed veal production.

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) that is approved for use as an anti-inflammatory, antipyretic (fever-reducer) and analgesic (pain-reliever) in cattle in Canada. The approved product is marketed as Metacam™ 20 mg/mL Solution for Injection (Boehringer-Ingelheim, Burlington, ON).

However, the label carries a warning stating not to use in veal calves as a withdrawal interval (i.e. the amount of time after the last treatment with the drug before the animal may be safely processed for consumption) has not been established in pre-ruminating calves. Therefore, the use of meloxicam in veal cattle is considered extra-label.

The VFO has partnered with the University of Guelph (Investigator Dr. David Renaud, Population Medicine and co-investigator Dr. Ron Johnson, Biomedical Sciences) on this project to provide data evaluating the tissue depletion and appropriate withdrawal interval for meloxicam in veal cattle based on Health Canada's approved Maximum Residue Limits (MRL; maximum allowable concentrations of drug in edible products of animals that will

ensure human food safety). Currently, there is no data evaluating the depletion of meloxicam in the tissues of veal cattle. This data, which will be generated by this study, could then be used by industry to better align with food safety and animal welfare programs, and procedures, as it is an effective product for treating veal cattle.

The project has been submitted to the Agricultural Adaptation Council and is scheduled for review in September. If approved, the study will begin immediately and wrap up by November 1, 2019.

This is an important step in ensuring veterinarians and producers have up-to-date research on the products that are being used in the veal cattle industry and are adhering to appropriate meat withdrawal times.

CGFARAD™ AND OTHER FOOD SAFETY RELATED RESEARCH

Dr. Ron Johnson, Co-director, CgFARAD™

CgFARAD™ secured a Growing Forward 2 grant (2016-2017) through the Livestock Research Innovation Corp. to establish a state of the art tissue culture suite in the Department of Biomedical Sciences at the Ontario Veterinary College, University of Guelph. Current research projects in the new lab involve the evaluation of risks of violative drug residues in poultry from extra label drug use combinations administered in feeds. The project is being funded by the Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA) Food Safety Research Program and CgFARAD™ stakeholders. The initial objective of the project is to establish functional poultry (turkey, chicken) hepatocytes in vitro.

CgFARAD™ Role and Mandate

- CgFARAD™ protects the Canadian food supply from unsafe or violative drug and chemical residues by providing expert advice to veterinarians on recommended withdrawal intervals.
- Veterinarians are legally permitted to prescribe drugs in an extra label manner but must provide new withdrawal guidelines.

CgFARAD™ personnel also assist:

- veterinarians in determining safe recommended withdrawal intervals when animals are accidentally exposed to pesticides, heavy metals or other chemicals;
- feed mills and processors when accidental contamination of feeds occur; and,
- regulatory agencies seeking clinical pharmacological expertise regarding drug residues.

In the second objective, isolated hepatocytes from control (drug-free) birds will be seeded onto multi-well culture dishes. Drugs of interest determined from review of the CgFARAD™ database that are used in combination in poultry feed and are not considered compatible in the Compendium of Medicating Ingredients Brochure of the CFIA will be applied alone and in combination at varying concentrations. Drug depletion (hepatic clearance) from the media will be measured over time using validated HPLC or HPLC-MS/MS assays. Results of this project will assist the CgFARAD™ pharmacology service with identifying combinations of drugs being requested for use in poultry feed that are at risk of violative residues from drug-drug interactions.

In addition to the research being conducted in the new lab, there is a study looking at drug depletion of injectable Trimethoprim Sulfa in lactating dairy does. Investigator Dr. Cathy Bauman (Population Medicine, University of Guelph) and co-investigator Dr. Ron Johnson (Biomedical Sciences, University of Guelph) have submitted a letter of intent to the OMAFRA-University of Guelph Partnership Research Program-Animal Production Systems theme for consideration of funding. Industry support for this study has been requested and is pending.

APIs AND COMPOUNDED PRODUCTS

Dr. Trisha Dowling and Dr. Ron Johnson, Co-directors, CgFARAD™

Active pharmaceutical products (APIs) are the raw chemical forms of a drug. In most instances, it must be formulated into a final drug product by the addition of one or more excipients. Excipients are substances included for the purposes of stabilizing the API (to give it a long “shelf-life”), increasing the bulk of APIs that are potent in very small amounts, or to improve the API in the final dosage form by improving its solubility and absorption.

Canadian pharmaceutical manufacturers may start an approved drug formulation with an API, add in excipients and end up with a proprietary (“brand name”) drug that is approved by Health Canada and assigned a Drug Identification Number (DIN). If the API molecule is no longer patent protected, generic versions may be made by other drug manufacturers. In order for a generic drug to receive approval and a DIN, the generic manufacturer must prove to Health Canada that the generic drug is bioequivalent to the proprietary drug by conducting very specific studies to prove that that they are interchangeable. Good quality bioequivalence studies demonstrate safety, efficacy, and potency of a generic drug and give prescribers confidence in such products.

When APIs are used to create drug products that do not follow the Health Canada procedures for an approved drug, the products should be referred to as compounded drug products. Unlike the United States, where pharmaceutical compounding is federally codified, veterinary drug compounding in Canada is guided by Health Canada policy, provincial veterinary and pharmacy regulations, and guidelines from the National Association of Pharmacy Regulatory Authorities (NAPRA) and the Canadian Veterinary Medical Association (CVMA).

The CgFARAD™ is unable to provide withdrawal guidance on compounded drug products in animals because these products are not assessed by Health Canada for their quality, purity, stability, bioavailability or efficacy. There are numerous publications of the analysis of compounded drug products that have found such products rarely meet standard specifications. In some cases, the concentrations are higher than stated (leading to potential toxicity) and in some cases, they are lower (leading to inefficacy). Other studies have demonstrated poor stability and “shelf-life” compared to proprietary and generic drug products. Without accurate data on the composition and bioavailability of a compounded drug product, it is impossible for the staff of the CgFARAD™ to determine the drug behavior and ultimate residue depletion profile when such a product is used in a food animal. Even if one compounding drug facility did the work to provide such data to the CgFARAD™, it could not be extrapolated to compounded drug products from other facilities as there can and will be differences in formulation.

Veterinarians should be aware that Canadian global Food Animal Residue Avoidance Databank (CgFARAD™) will not provide advice on withdrawal periods for compounded drugs.