Animal Drug Residues in Food

Food Toxicology
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Learning Objectives

- Define animal drug residues.
- Explore the relationships between food animals and drugs.
- Understand the major classes of drugs used in food animals.
- Understand the hazards associated with food animal drug use and how risk assessment is used to determine tolerances.

Learning Objectives

- Review the role of pharmacokinetics in the development of withdrawal times.
- Review food animal drug testing results.
- Understand the potential adverse effects of drugs that appears as residues in food animals.
- Discuss the issue of development of antibiotic resistant bacteria.

Animal Drug Residues

- *"Residues of veterinary drugs include the parent compounds and/or their metabolites in any edible portion of the animal product, and include residues of associated impurities of the veterinary drug concerned."*

Food Animals - Food Animal Health - Drugs

- Food animals convert one source of nutritional energy (grass, grain, hay) into another (meat, milk, eggs).
- Food animal production practice requires management of animal health and this can require the use of drugs.
  - Animal health management
  - Animal industry economics

- Human health effects of food animal drugs can arise from drug residues.
- Human health effects can also arise when food animal drugs are not used (pathogens).

Meat, Fish, and Dairy Consumption

- The average American consumes 200 pounds of meat and fish, 67 pounds of poultry, 30 pounds of eggs, and 600 pounds of dairy products each year.
- Drug residues are analyzed, regulated, and monitored by FDA-CFSAN/CVM, USDA-FSIS, state milk ordinances, JEFCA (Joint FAO/WHO Expert Committee on Food Additives), international food agencies.
- Veterinary drugs are used by veterinarians and by food animal producers.
  - Pre-market drug tests
  - Residue avoidance testing
  - Drugs labels

Food-Producing Animal Species

- Major species
  - Cattle, cows
  - Swine
  - Chickens
  - Turkeys
- Minor species
  - Sheep
  - Goats
  - Llamas/Alpacas/Camels
  - Deer and other wildlife
  - Others

Major Classes of Drugs Used in Food Animals

- Topical antiseptics, bactericides, and fungicides
- Ionophores
- Steroid anabolic growth promoters and peptide production enhancers
- Antiparasite drugs
- Antibiotics

Other Food Animal Drugs

- Drugs that modify the gastrointestinal environment to reduce the likelihood of rumen foaming and bloat in cattle.
- Organic and inorganic water treatments that reduce the chances for water or fish infection in aquaculture.
- Miscellaneous drugs and compounds used with the advice of veterinarians to treat specific conditions.

Topical Antiseptics-Bactericides-Fungicides

- Used to treat surface skin, or hoof infections, cuts, and abrasions.

Ionophores

- Alter rumen microorganisms to provide more favorable and efficient energy substrates from bacterial conversion of feed.
- Impart some protection against some parasites.

Steroid Anabolic Growth Promoters and Peptide Production Enhancers

- Mechanism of action resides in the interaction of estrogen-, progesterone-, or testosterone-like compounds with specific classes of hormone receptors in animal cells.
  - Recombinant bovine somatotropin (BST) for increased milk production in dairy cows.

Antiparasite Drugs

- Used to control fleas, ticks, mange (mites), worms, giardia, coccidia and other intestinal parasites.

Antibiotics

- Used to control overt and occult (sub-clinical) diseases.
- Used to promote growth in sub-therapeutic doses.

Drugs in Food-Producing Animals

- Potentially dangerous residues in food of animal origin.
- Risk and benefits analysis required.
- Risk modifiers include “withdrawal time” and “residue avoidance practice.”

Human Health Risk Issues

- Drug residue allergy
- Cancer, reproductive, and developmental effects

- Hormones
- Development of antibiotic resistant microbes
- Drug misuse

Animal Drug Residue Tolerance Levels
Tolerance: Hazard Identification

- Short term
  - Allergenicity
  - Toxicity
- Long term
  - Microbiological effects
  - Carcinogenicity
  - Reproductive effects
  - Teratogenicity

Toxicity: Clenbuterol

- Non-steroidal anabolic and metabolism accelerator.
- Spain, 1990 outbreak: 135 people ill from eating contaminated liver.
  - Several hospitalizations: tachycardia, muscle tremors, headaches, nausea, fever, chills
- Jalisco Mexico, December 2005: at least 225 people ill after consuming beef/liver.
  - Trembling, headache and malaise

Allergenicity: β-Lactam Antibiotics

- Anaphylactic reactions have been reported to result from consumption of beef or pork containing penicillin.

Microbiological Effects

- Disruption of normal human flora in the intestine.
  - Bacteria that usually live in the intestine act as a barrier to prevent incoming pathogenic bacteria from getting established and causing disease.
- Antibiotic residue might reduce total numbers of these bacteria or selectively kill some important species.

Carcinogenicity: Nitrofurans, Nitroimadazoles

- Furazolidone and its metabolites have been shown to induce cancer in animals.
- Had been labeled and approved for anti-protozoal and other uses for a wide variety of conditions in poultry and swine.
- FDA approval withdrawn 1991.
- FDCA Delaney Clause.

Reproductive and Teratogenic Effects: DES

- Diethylstilbestrol: a synthetic estrogen formerly used commercially as a growth promoting agent in livestock.
- Drug used in pregnant women in 1940's.
  - Vaginal clear-cell adenocarcinoma in female off-spring exposed *in utero* (1 in 1000)
  - Structural abnormalities of uterus (69%)

Dose-Response and Exposure Assessment

- Toxicological tests in laboratory animals.
  - Part of pre-clinical drug development.
- Development of NOAEL.
- Safety factors.
- Acceptable daily intake (ADI).
- Sub-population sensitivity.
- Exposure assessment.
  - Food consumption.
  - Aggregate exposure.
- Use to develop *Tolerance Level.*

Tolerance Level

- The maximum permissible residue level which may be present in tissues or food animal products.
- Tolerances are specific for species and tissue (liver, kidney, fat, muscle) or product (milk, eggs).

Withdrawal Time

- Time required for a drug or chemical concentration to fall below the *Tolerance Level* established in a specific target animal tissue.
- Dependent upon drug, dose, formulation, route of administration, species, target tissue and disease / management factors.
- Pharmacokinetics-toxicokinetics of the drug is the main factor.
  - Therapeutic level vs. elimination

- PK of elimination can be different for different tissues.

Animal Drug Withdrawal Time

Animal Drug Withdrawal Time

- Experimentally determined.
- Time required that concentrations in all food animal tissues or products are below tolerance.
- Margin of safety (MOS) increased to 95% confidence interval for 99% of population.
  - MOS = LD_1/ED_{99}
- Expensive
  - Limited products
  - Healthy animals

Animal Drug Withdrawal Time

- Other considerations
  - Aesthetic considerations
  - Risks perceived by public
  - Sensitive populations and issues
  - International relations and trade barriers

Extralabel (Off-Label) vs. Label Drug Use

- Higher dose than label
- Different route than label
- Different species than label
- Different disease indication than label

AMDUCA 1996

- Animal Medicinal and Drug Use Clarification Act 1996
- Permits extralabel drug use in animals
  - Does not apply to feed and water additives
  - Several drug classes have been excluded
- Some drugs are prohibited from use in food animals
  - Clenbuterol, chloramphenicol, nitroimidazoles, nitrofurans
- Withdrawal time extrapolations from other known applications
  - WDT = 10 x $T_{1/2}$

Over-The-Counter (OTC) Veterinary Drugs

- Majority of animal drugs sold in US
- Can still cause residues if not used according to label.

Drug Residue Testing

- Target tissues tested
  - Milk
  - Kidneys often tested at slaughter
- STOP
  - Swab test on premises
- FAST
  - Fast antimicrobial screen test
- SOS
  - Sulfa-on-site
- CHARM II; SNAP
  - Milk residues
- Lab tests
  - HPLC/GC/Mass Spectrometry

FDA Milk Drug Residue Database 2003

- 4,382,974 samples were analyzed for animal drug residues.
- 2,945 were positive for a residue.
- Samples:
  - Bulk Milk Pick-Up Tanker
    - Bulk raw milk from a dairy farm
  - Pasteurized Fluid Milk and Milk Products
    - Finished product in package form or bulk
  - Producer

FDA Milk Drug Residue Database 2003
Milk Residue Screening by Drug Family
2003 FSIS Meat Residue Monitoring

- Penicillin and sulfonamide drugs were most commonly detected at violative levels in swine and cattle.
- Neomycin and gentamicin were also detected in a number of cattle, particularly calves.
- Other drugs detected in cattle and swine included tilmicosin, flunixin, and tetracyclines.
- Arsenicals were detected in poultry.

Drugs Most Likely to be Detected in Meat

- Penicillin (including ampicillin)
- Tetracycline (including chlortetracycline and oxytetracycline)
- Sulfonamides (including sulfadimethoxine and sulfamethazine and sulfamethoxazole)

- Neomycin
- Gentamicin
- Flunixin
- Streptomycin
- Arsenicals

Penicillin

- Penicillin derivatives (β-lactam antibiotics) are widely used in cattle, swine and poultry to treat infections and as feed or drinking water additives to prevent some diseases.

Potential Adverse Effects: Penicillin

- Usually cleared rapidly from the blood via the kidneys and into the urine (kidney, liver about 100x higher than muscle).
- Allergic reactions determining factor for safety evaluation of residues.
  - Allergy to penicillin in different populations 3–10%.
  - No evidence that penicillin residues in food caused sensitization.
  - Some cases of persons with known sensitivity suffering allergic reaction
- Estimated that 10 IU (0.6 μg) could cause an allergic reaction in a sensitive individual.
  - 0.01 IU/ml of milk in a very sensitive individual.
- 2 cases of anaphylactic reactions with known hypersensitivity to penicillin, steak (in 1984) and pork (in 1972).
- JECFA estimated that if residues in meat (including liver and kidney) were at the MRL of 0.05 mg/kg and for milk were 0.004 mg/kg, the maximum daily intake of benzylpenicillin from residues would total 29 μg.

Tetracyclines

- Oxytetracycline is a broad-spectrum antibiotic used to treat a variety of infections and is also used as a growth promoter in animals.

Potential Adverse Effects: Tetracyclines

- Humans, ~ 60% of an ingested dose absorbed from GIT and widely distributed in the body.
  - Particularly to liver, kidney, bones and teeth.
  - Little metabolism of this drug in humans or animals and it was primarily excreted in the urine
- Not mutagenic, carcinogenic, or teratogenic in animal studies; some toxic effects were observed at high doses.
  - NOAEL 18 mg/kg body weight/day.
- Therapeutic doses occasionally associated with discolored teeth, allergic reactions, or peripheral blood changes
- Oxytetracycline did induce antibiotic resistance in coliforms in the human intestine; JECFA used this for MRL.
  - NOEL 2 mg/person/day

- There have been reports of allergic reactions but no cases that have involved exposure to residues in foods.
- JECFA estimated that if OTC residues in meat, milk and eggs were at the MRL. residues would total 260 µg.

Sulfonamides

- Sulfonamides are generally used to treat a wide variety of bacterial and coccidial infections in food producing animals and are used as growth promoters in swine.

Potential Adverse Effects: Sulfonamides

- Metabolized by numerous pathways with the major metabolite in humans, swine and cattle being an acetyl derivative.
- Data cited by JECFA indicate that the primary mechanism of toxicity of sulfonamides is associated with the thyroid–hypothalamus
  - Toxicity should be measured by parameters of thyroid and pituitary function.
- NOAEL 2.2 mg/kg bw/day.
- Hypersensitivity reactions (primarily skin rashes) to therapeutic levels of sulfonamides have been reported but there have been no cases that involved exposure to residues in foods.

Neomycin

- Neomycin is an aminoglycoside antibiotic that is used to treat intestinal, respiratory, and wound infections and mastitis.

Potential Adverse Effects: Neomycin

- Neomycin is not readily metabolized in animals or in humans.
- Not genotoxic. Like streptomycin and gentamicin, it has been reported to cause damage to the kidney and to hearing.
  - Recent data indicate that people with a rare mutation in their mitochondrial DNA may be more susceptible to deafness caused by aminoglycosides and other environmental factors than the general population.
- JECFA based its recommendation for a maximum daily intake of 3.6 mg/kg bw on results on hearing loss in guinea pigs.
- JECFA calculated that the estimated dose of neomycin from veterinary drug residues was 3 mg/day, primarily from milk (2.25 mg), kidney (0.5 mg), and muscle (0.15 mg). This was 3000 times less than the recommended oral therapeutic dose of neomycin.

Gentamicin

- Gentamicin is an aminoglycoside antibiotic

Potential Adverse Effects: Gentamicin

- Like streptomycin and neomycin, gentamicin has been reported to cause damage to the kidney and to hearing.
- Depleted rapidly from muscle and fat but tends to persist in kidney and liver.
- Not readily metabolized in animals or in humans.
- JECFA estimated that if residues in meat were at the recommended MRL, the maximum daily intake of gentamicin from residues would total 785 µg.

  - 30 µg from muscle, 200 µg from liver, 250 µg from kidney, 5 µg from fat, 300 µg from milk.

Flunixin

- Flunixin is a non-steroidal anti-inflammatory drug (NSAID) and analgesic and is the only such drug allowed for use by veterinarians.

Potential Adverse Effects: Flunixin

- Flunixin inhibits prostaglandin synthesis apparently by a mechanism similar to aspirin.
- Since NSAIDs are commonly used in human medicine, it is believed that flunixin is a relatively safe drug and residues should not be very harmful.
- However it appears that this drug has not been tested adequately on humans, particularly for hypersensitivity reactions.

Streptomycin

- Streptomycin is an aminoglycoside antibiotic used for treating bacterial infections in food producing animals.

Potential Adverse Effects: Streptomycin

- Not readily absorbed from the GIT because of its high molecular mass and not metabolized significantly w/ inj.
- Oral doses of the drug are eliminated unchanged in the feces.
- Animal studies indicate most sensitive end point was a decrease in weight; used to set ADI of 30 µg/kg bw.
- Reports of allergic reactions to streptomycin
  - No cases that have involved exposure to residues in foods.
- One significant adverse effect in humans that occurred during treatment of pregnant women with TB.
  - Infants of women treated IM 1 g BIW 1st trimester: damage to a cranial nerve and congenital deafness.
- Streptomycin may also have adverse effects on kidney fn.
- No other evidence of effects on fertility or reproduction.
- It is not expected that low food residues/low abs. would affect fetal development.

Arsenicals

- Arsenical compounds are used in swine and poultry as growth promoters and to prevent bacterial enteritis.
- The most commonly used arsenic compound for poultry is roxarsone.

Potential Adverse Effects: Arsenicals

- Most of the roxarsone is excreted unchanged, but some metabolites have been detected in hen urine.
- Roxarsone is poorly retained in poultry meat (FDA limit is 0.5 mg/kg in chicken muscle).

- Inorganic arsenic is a known carcinogen and may adversely affect the circulatory and nervous systems.
- Organic arsenic is generally less toxic and some arsenic compounds are considered harmless.
- Diets containing 800 mg/kg roxarsone caused decreased body weight in mice; rats were more sensitive, showing lower body weights on diets containing 200–400 mg/kg roxarsone.
- There was equivocal evidence for carcinogenicity in male rats fed 100 mg/kg roxarsone for 2 years, but no evidence of carcinogenicity in female rats and both sexes of mice.

Development of Antibiotic-Resistant Bacteria

- Bad bugs → no drugs
- A major issue of drug use in food animals as well as over-use of antibiotics in humans

Antibiotic-Resistant Bacteria Isolated From Meat

- Hypothesis was that the greater the amount of a drug used, the more likely bacteria would develop resistance to it.
- Beef:
  - Tetracycline > streptomycin = sulfamethoxazole > ampicillin > chloramphenicol > cephalothin
- Pork:
  - Tetracycline > streptomycin = sulfamethoxazole > ampicillin > chloramphenicol > gentamicin
- Chicken:
  - Tetracycline > sulfa > streptomycin = cephalothin > ampicillin > chloramphenicol > gentamicin
- Turkey:
  - Sulfamethoxazole > tetracycline > streptomycin > ampicillin > cephalothin > gentamicin

Less Antibiotic Use In Food Animals Leads To Less Drug Resistance In People

- *Campylobacter jejuni* is a leading bacterial cause of foodborne illness in industrialized countries.
- Drug resistance can make Campylobacter infections difficult for to treat, and can result in longer bouts of and a higher risk of serious or even fatal illness.
- Australia prohibited the use of fluoroquinolones, in food animals such as poultry.
- Researchers examined *C. jejuni* isolates collected from 585 patients in five Australian states.
- Only 2% of the locally acquired Campylobacter isolates were resistant to ciprofloxacin, a type of fluoroquinolone (29% in countries w/o ban).
  - Sweden prohibited the use of fluoroquinolones for food animals in 1986
  - Norway has never licensed their use in food animals
- FDA proposed banning fluoroquinolones in poultry in 2000; finally enacted in September 2005.

Animal Drug Residue Concerns

- Consumer health risk
  - Environmental concerns
- Consumer preference
- Production loss for the producer
  - Lost milk product ($6,000 to $80,000)
  - Lost animal ($500 to $2000)
- Legal action against the producer
  - Violative (illegal) residues