Dogs and cats are not small people: An introduction to dispensing for veterinary patients

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Disclosures

• Royalty Income (U.S., Europe, Australia, NZ)
  ▪ MDR1 Genotyping for Dogs

• Pfizer Animal Health
  ▪ Consulting/Advisory Board

• Bayer Animal Health
  ▪ Consulting/Advisory Board
Objectives

• List species that FDA considers ‘Food Animals’ and provide rationale for banning of some drugs in food animals

• Describe some species differences in Drug...
  – Absorption
  – Distribution
  – Metabolism
  – Excretion
Objectives

• Understand implications of pharmacogenetics in veterinary patients

• Understand limitations of human ADR and drug-interaction software for veterinary patients
Outline

• Regulation of Veterinary Drugs
  ▪ Companion Animals
  ▪ Food Animals

• Species PK Differences
  ▪ Absorption
  ▪ Distribution
  ▪ Metabolism
  ▪ Excretion

• Limitations of Human Software in Predicting Veterinary ADRs and Drug Interactions
Jargon

• Small Animal
  - Laboratory Research/Drug Development
    - Rodents
  - Practicing Veterinarians
    - Dogs, cats, pocket pets and exotics

• Large Animal
  - Laboratory Research/Drug Development
    - Dogs, cats, primates
  - Practicing Veterinarians
    - Horses, Livestock (including camelids)
Jargon

• “Companion” Animals
  - Dogs
  - Cats
  - Horses
“Companion” Animals

- Minor Species: ‘pocket pets’ and other exotics
Food (food-producing) Animals (U.S.)

- Cattle
- Sheep
- Pigs
- Poultry
- Fish
- Other mammals (goats, buffalo, etc.)
- Honey bees

- NOT horses
Food (food-producing) Animals (U.S.)

- Considerations: Withdrawal time and avoidance of tissue residues

Gentamicin is detectable in tissues for 18 months! No approved use for food animals.

Pharmacists may receive inquiries about OTC drugs for food animals—consider withdrawal time!!
Food and Drug Administration (FDA)

• Federal agency
• Regulates drug use in veterinary and human medicine
  ▪ Approves new drugs
    – Safety and Efficacy
FDA Center for Veterinary Medicine

- Drug Safety*
  - Animal
  - People (food)
  - Environment
- Efficacy
  - Consistently performs as claimed on label

*Safety: Depends on drug indication. Greater risk of adverse effects tolerated for drugs intended to treat life-threatening
FDA—Drug Safety

• Spinosad
  • Nicotinic acetylcholine receptor agonist
  • Indication: prevention of fleas
  • Mild GI toxicity
    • No greater than control

• SU11486
  • Tyrosine kinase inhibitor
  • Indication: tx mast cell tumors in dogs
  • GI (80%)
  • Neutropenia (7%)
  • Neuromuscular (30%)
Physostigmine
- Cholinesterase inhibitor

Owner had acute (fatal) asthma attack while shampooing dog
FDA—Drug Safety

- Tilmicosin (Micotil™)—Human Toxicity
  - 3,168 human exposures → 44% clinical
    - 5% involved serious adverse effects
      - Cardiac/cardiovascular
    - 13 deaths (11 intentional; 2 accidental)
    - 2 accidental = IM injection (estimated 10ml)

Veenhuizen et al, J Am Vet Med Assoc 2006;229:1737
Food and Drug Administration (FDA)

- Non-FDA-approved “drug” use:
  - Extralabel drug use
  - “Nutraceuticals”
  - Compounded drugs
FDA Regulations

- Veterinary*-Client-Patient Relationship

Valid VCP relationship exists when
  - DVM has assumed responsibility for making clinical judgements regarding the health of an animal(s)
  - DVM has determined the need for medical treatment
  - Client has agreed to follow the DVM’s instructions
  - DVM has enough information about the animal(s) to make a preliminary diagnosis (recently examined)
  - DVM available for followup (adverse reactions/failure to respond)
Extralabel Use of Veterinary Drugs

- Use of a drug in a veterinary patient in a manner that is not in accordance with FDA-approved labeling
- MUST be in context of valid VCP relationship
- Different species
- Different dose or dose interval
- Different route of administration
- Different disease
- Different withdrawal time
Extralabel Use of Veterinary Drugs

• Example:

**INDICATION**
SIMPLICEF tablets are indicated for the treatment of skin infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus intermedius*, *Staphylococcus aureus*, *Streptococcus canis* (group G, β hemolytic), *Escherichia coli*, *Pasteurella multocida*, and *Proteus mirabilis*.

- Extralabel
  - Cat
  - Klebsiella Sp
  - UTI in a dog
Extralabel Use of Veterinary Drugs

• FDA’s perspective--NON food animals
  ▪ No FDA approved drugs for some diseases/conditions
  ▪ Allow DVMs to use professional judgment
  ▪ Valid VCP relationship
  ▪ Human drugs allowed
    – No veterinary drug approved
    – Health of animal threatened
  57 in a 55…I’ll let ‘em slide.
Extralabel Use of Veterinary Drugs

- FDA’s perspective—Food Animals
  - Need to be much more careful
  - STRICT attention to withdrawal times
  - Avoid list of prohibited drugs
Compounded Veterinary Drugs

• Limited situations
  ▪ Must be a need* based on VCP relationship
  ▪ No FDA approved veterinary or human drug available
  ▪ Should be safe and effective
  ▪ For food animals—extended withdrawal time
  ▪ No Bulk Drugs

*Animal’s life threatened; suffering will occur without medication
The deaths of so many horses in a single day has cast a pall over the Open, which resumed Thursday in Wellington, Fla.
Compounded Veterinary Drugs

• Disadvantages vs FDA-approved drugs
  ▪ Not tested for safety and efficacy
  ▪ Manufacturing process not monitored
    – Strength/concentration
    – Purity
  ▪ Stability of final product
  ▪ Lack of adverse event reporting system
Adverse Event Reporting

• FDA
  ▪ http://www.fda.gov/cvm/adereporting.html

• Manufacturer
Special Considerations for Food Animals

• Safe food supply high priority for FDA
• Drugs that have been determined to pose potential danger to food supply **banned** for extralabel use in food animals
  - Chloramphenicol
  - Clenbuterol
  - Diethylstilbestrol (DES)
Special Considerations for Food Animals

- Drugs that have been determined to pose potential danger to food supply banned for extralabel use in food animals
  - Dimetridazole
  - Ipronidazole
  - Other nitroimidazoles (metronidazole)
  - Furazolidone (except for approved topical use)
  - Nitrofurazone (except for approved topical use)
Special Considerations for Food Animals

- Drugs that have been determined to pose potential danger to food supply banned for extralabel use in food animals
  - Sulfonamides in lactating dairy cattle
    - Except approved uses of
      - Sulfadimethoxine
      - Sulfabromomethazine
      - Sulfaethoxypyridazine
Special Considerations for Food Animals

- Drugs that have been determined to pose potential danger to food supply banned for extralabel use in food animals
  - Fluoroquinolones
  - Glycopeptides

- Recently added
  - Adamantanes and Neuroaminidase inhibitors for Poultry
  - Cephalosporins (July 2008)
Prescription Writing Problems to Avoid

- FDA
  - A Microgram of Prevention is Worth a Milligram of Cure: Preventing Medication Errors in Animals

- [http://www.fda.gov/AnimalVeterinary/ResourcesforYou/](http://www.fda.gov/AnimalVeterinary/ResourcesforYou/)
Prescription Writing
Problems to Avoid

• FDA
  - A verbal prescription for a dog for “Leukeran 2 mg SID for 10 days” was transcribed as “BID for 10 days.” The dog was administered the drug twice daily for 10 days and died. The abbreviation “SID” was unfamiliar to the pharmacist.
Prescription Writing Problems to Avoid

• FDA
  • A written prescription for a cat for “Ursodiol 250 mg tablet, give ½ tablet SID” was misinterpreted as “give ½ tablet QID.” The cat received an overdose for two days, but fortunately, only experienced diarrhea.
Other Agencies Regulating Veterinary “Drug” Products

- Topical heartworm preventives
  - FDA

- Topical flea preventive
  - EPA
  - “Pesticide”

- Oral flea preventive
  - FDA
• Which of the following animal(s) would be considered a “food” animal from a regulatory (FDA) perspective?
  A. Horse
  B. Pet pot-bellied pig
  C. Mouse raised to be fed to snake
  D. 4-H Dairy Cow

• What extra burden of safety does the FDA CVM require of pharmaceutical companies that produce drugs for food animals?
• What is a common abbreviation used by veterinarians in prescription writing that is intended to mean “once a day”?

• Why is chloramphenicol prohibited for use in food animals?

• Why is extralabel use of fluoroquinolones prohibited in food animals?
Species differences in drug Absorption

- Absorption
  - Movement of drug from site of administration to systemic circulation

- IV administration = no drug absorption

- PO, SQ, IM = absorption does occur therefore resulting in some delay in drug action
Species differences in drug absorption

- Oral Absorption
  - Horses
    - Nonglandular portion of stomach (squamous epithelium) – non absorptive
    - Many drugs have low oral bioavailability
Species differences in drug absorption

- Oral Absorption
  - Adult Ruminants (cattle, sheep, goats)

Poor oral drug absorption!!
Drugs with species differences in oral bioavailability

- Prednisone
  - Active form is prednisolone
  - Horses and cats have low oral bioavailability of prednisolone after administration of prednisone
    - Should receive prednisolone rather than prednisone
Drugs with species differences in oral bioavailability

- Fludrocortisone (Florinef®)
  - Oral bioavailability lower than in people
    - Human dose = 0.1 mg/adult/day
    - Canine dose = 0.1 mg/10kg body weight/day
Drugs with species differences in oral bioavailability

- Synthetic T4 (Levothyroxine)
  - Bioavailability low in dogs
  - 0.075 to 0.125 mg/person/day
  - 0.2 mg/10 kg dog/day

Human formulation
Drugs with species differences in oral bioavailability

- Oral Bioavailability of Ciprofloxacin
  - Human-high
  - Dog-variable but tends to be low
  - Horse-variable but tends to be low

No veterinary approved ciprofloxacin products

Some owners/veterinarians/pharmacists consider cipro instead of approved veterinary formulations (generic version is cheap).

Not equivalent to veterinary formulations.
Species differences in drug distribution

• Distribution
  ▪ Movement of drug from systemic circulation to tissues (site of action).

  ▪ Protein binding, water/lipid solubility, and drug size (molecular weight) are important factors affecting a drug’s Vd

  ▪ Drug transporters are also important factors affecting a drug’s distribution
Species differences in drug distribution

- Distribution—tissue barriers (Drug Transporters)
  - Some tissues are more protected than others
    - Testes
    - Placenta
    - Prostate
    - Eye (blood retina barrier)
    - Brain (blood brain barrier)
Blood-Brain Barrier—ABCB1 (MDR1) gene

- Astrocyte foot processes
- P-glycoprotein
- Neuron
- Xenobiotic

Capillary Lumen
ABCB1 (MDR1) gene and BBB defect

• “Ivermectin Sensitivity” in Collies*
  ▪ Reported in 1980’s
  ▪ Subsequently reported in other herding breed dogs

• “White feet, don’t treat!”

*Extralabel use: doses $\geq 20$ X label dose
ABCB1 as candidate gene

Ivermectin Sensitivity in Collies

- Ivermectin is substrate for P-gp

- Abcb1(-/-) mice develop neurotoxicity if treated with ivermectin
**ABCB1 Polymorphism**

275
TGGTTTTTTGAAACATGACAGATAGCTTTGCAAATGCAGGAATTTCAAGAAACAAAACTTTT
TGGTTTTTTGAAACATGACAGATAGCTTTGCAAATGCAGGAATTTCAAGAAACAAAACTTTT

337
CCAGTTATAATTAATGAAAGTATTACGAACACATACACAACATTTTCAATACACCACATCTGGAGGA
CCAGTTATAATTAATGAAAGTATTACGAACACATACACAACATTTTCAATACACCACATCTGGAGGA

399
GGAAATGACCCACGTATGCCTATTATTACAGTGACCGGTGTGCTGCCGTGCTGCTGGCTGCTTT
GGAAATGACCCACGTATGCCTATTATTACAGTGACCGGTGTGCTGCCGTGCTGCTGGCTGCTTT

461
ACATCCAGGTTTTTCACTTCCTGGTCATGCCTGGCAGTCAGGAAGACTGCTAAATTAGAAAACAAA
ACATCCAGGTTTTTCACTTCCTGGTCATGCCTGGCAGTCAGGAAGACTGCTAAATTAGAAAACAAA

523
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TTTTTTTCTATGCTATCATGCAGGAAGATTGCGTCTCTGCTGGCGTGCTGGTGGCTGCTT

585
TAACACCCGGCTCACAGACGATGTCTTCTCCAAAATCAATGAGGAATTTGCGACAAAAAGTTGGAA
TAACACCCGGCTCACAGACGATGTCTTCTCCAAAATCAATGAGGAATTTGCGACAAAAAGTTGGAA

647
TGTTTTTTTACATCATTACACACATTTTTACACCCGTTTTTATAGTGCGGGGGTTTACACGTGGTT
TGTTTTTTTACATCATTACACACATTTTTACACCCGTTTTTATAGTGCGGGGGTTTACACGTGGTT
P-glycoprotein (Wildtype)

- ATP binding sites
- Substrate binding sites
P-glycoprotein (in dogs with MDR1 mutation)
Blood-Brain Barrier Wildtype

- Astrocyte foot processes
- P-glycoprotein
- Neuron
- Xenobiotic
Blood-Brain Barrier
ABCB1 (MDR1) mutation

Capillary Lumen

- Astrocyte foot processes
- P-glycoprotein
- Neuron
- Xenobiotic
Nuclear Scintigraphy
99mTc Sestamibi

ABCB1 Wildtype

ABCB1 mut/mut
ABCB1 Pharmacogenetics
Clinical Perspective

• Macrocyclic Lactones (Antiparasitics)
  ▪ Severe, prolonged CNS Toxicity

• Loperamide
  ▪ CNS Toxicity

• Vincristine
  ▪ Myelosuppression

Drug Metab Disp 2008;36:1073.
MDR1 (+/+) No drug
MDR1 (+/+): Loperamide 0.2 mg/kg oral
4 hours
MDR1 (-/-) No drug
MDR1 (---) Loperamide 0.2 mg/kg oral 4 hours
MDR1 (+/+) Loperamide 0.2 mg/kg oral
4 hours: Naloxone injection
Metabolism

• Phase I
  ▪ Oxidative reactions
    – CYP
  ▪ Reduction
  ▪ Hydrolysis

• Phase II
  ▪ Conjugative reactions
    – Glucuronidation
    – Acetylation
Species differences in Drug Metabolism

- Dogs
  - Deficient (absent) N-acetyl transferase
    - Hydralazine
    - Procainamide
    - Isoniazid
    - Sulfonamides
Species differences in Drug Metabolism

• Cats
  - UDP glucuronidation
    - Acetaminophen
      • NO SAFE DOSE FOR CATS
      • Erythrocytes highly susceptible to oxidative injury
    - Aspirin
      • LOW dose every 72 hours
  - Morphine
  - Ibuprofen
  - Chloramphenicol, others
Species differences in Drug Metabolism

<table>
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<tr>
<th>DRUG</th>
<th>Human $t_{1/2}$</th>
<th>Dog $t_{1/2}$</th>
<th>Cat $t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2.3 hours</td>
<td>4.5 hours</td>
<td>22 hours</td>
</tr>
<tr>
<td>Propofol</td>
<td>1.9 hours</td>
<td>2.4 hours</td>
<td>8.8 hours</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>47 hours</td>
<td>40 hours</td>
<td>11 hours</td>
</tr>
</tbody>
</table>

Individual and breed differences exist
Excretion

- Renal
  - GFR
  - Active secretion
- Biliary
  - Transporters
ABCB1 Pharmacogenetics
Clinical Perspective

• Macrocyclic Lactones
  ▪ CNS Toxicity

• Loperamide
  ▪ CNS Toxicity

• Vincristine*
  ▪ Myelosuppression

*Highly dependent on biliary excretion
ABCB1 Genotype and Vincristine-associated Neutropenia in Dogs with Lymphoma

VCOG Neutropenia Score

0 neutrophils/\mu l

[Graph showing comparison between ABCB1-1Delta and ABCB1 Wildtype for VCOG Neutropenia Score]
Nuclear Scintigraphy
99mTc-Sestamibi

Time-60 minutes after IV injection

MDR1 Wildtype

MDR1 mut/mut

Gall bladder
ABCB1 (MDR1) Pharmacogenetics
Clinical Perspective

Biliary Excretion of $^{99m}$Tc-sestamibi in dogs
Breed Distribution: over 30,000 dogs genotyped
ABCB1 (MDR1) Pharmacogenetics Clinical Perspective

- Pharmacogenetic Testing
  - Veterinary Dermatologists
    - Mange
      - Ivermectin
      - Milbemycin
  - Veterinary Oncologists
    - Chemotherapy
      - Vincristine
      - Doxorubicin
- Owners
- Breeders
ABCB1 (MDR1) Pharmacogenetics

Drug Interactions

• Many drugs inhibit P-gp
  ▪ Ketoconazole

Intrinsic P-gp deficiency → Polymorphism

Extrinsic P-gp deficiency

Collie-morphism
P-gp inhibitor
P-gp inhibitor
P-gp inhibitor
Review

• Describe factors that might adversely affect oral drug absorption in:
  - Horses
  - Cattle
Review

• List a species-wide metabolic defect (and an affected drug) in:
  ▪ Cats
  ▪ Dogs
Review

• Name a breed-related adverse drug reaction that is caused by a genetic mutation in a drug transporter and name 3 drugs that are affected by this mutation.
Protein Binding

- Protein binding
  - Highly species specific

- NSAIDS
  - 99%+ in most species
Other species-specific ADR’s

• Cats and Fluoroquinolones (FQ)
  • FQ-induced retinal toxicity in cats
    ▪ Clinical observations

  ▪ Experimental
    – Enrofloxacin
     • 50 mg/kg → retinal degeneration and blindness in 12/12 cats

Ford et al AJVR 2007
Enrofloxacin induced retinal degeneration

Tx day -1  3  5  7

Ford et al AJVR 2007
ABCG2 Candidate Gene

• Identified at blood-retina barrier (mice)*

• Enrofloxacin (and other FQ’s) are substrates

• FQ’s + UV light → ROS
  • Skin
  • Eye

*Asashima et al Pharm Res 2006
<table>
<thead>
<tr>
<th></th>
<th>Glutamate (Polar)</th>
<th>Methionine (Nonpolar)</th>
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<tbody>
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<td>Human</td>
<td>QFSAALRLATTMTNHEKNERINRVIQELGLDKVADSKVGT</td>
<td></td>
</tr>
<tr>
<td>Chimp</td>
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<tr>
<td>Macaque</td>
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<tr>
<td>Bovine</td>
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<td>Rat</td>
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</tr>
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<td>Mouse</td>
<td>QFSAALRLPTTMKNHEKNERINTIIKELGLEKAVADSKVGT</td>
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<tr>
<td>Dog</td>
<td>QFSAALRLPTTTSHEKNERINKVIQQGLGLDKVADSKVGT</td>
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</tr>
<tr>
<td>Cat</td>
<td>QFSAALRLPTTMTTNEKNMRINRVIQELGLDKVADSKVGT</td>
<td></td>
</tr>
</tbody>
</table>

Glutamate (Polar) → Methionine (Nonpolar)
Clinical Implications

• Cats receiving FQ’s should avoid exposure to light

• Drug interactions in other species could cause retinal toxicity
  - FQ’s + ABCG2 inhibitors
Other species-specific ADR's

- Pocket pets and oral penicillins/cephalosporins
- Intestinal overgrowth of *Clostridium* sp
Human adverse drug reaction monitoring systems

- Fail to account for species differences
- Fail to account for known pharmacogenetic or breed differences
- Do not include many drugs commonly used in veterinary patients
  - Antiparasitics
- Do not include other products commonly used in veterinary patients
  - Pesticides (flea/tick)
Today the U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) is announcing that it has received reports of adverse reactions in dogs receiving the drug Comfortis® (spinosad) concurrently with high, extra-label doses of the drug ivermectin. The clinical signs of these adverse reactions are consistent with ivermectin toxicity…

COMFORTIS® and ivermectin interaction Safety Warning Notification
June 24, 2008
Today the U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) is announcing that it has received reports of adverse reactions in dogs receiving the drug Comfortis® (spinosad) concurrently with high, extra-label doses of the drug ivermectin. The clinical signs of these adverse reactions are consistent with ivermectin toxicity…
FDA—Preferences in Drug Use

1. FDA approved veterinary drug according to label
2. FDA approved veterinary drug off-label
3. FDA approved human drug
4. Compounded drug
   ONLY if 1-3 are not possible AND the health of animal is threatened, or suffering or death may result from a lack of treatment