Selected Topics in Rational Antimicrobial Usage

Mark V. Crisman DVM, MS, DACVIM
Senior Veterinarian; Zoetis
Adjunct Professor; Virginia Maryland College of Veterinary Medicine

Dr. Alexander Fleming (1928) initiated the 'modern age of medicine' with the discovery of penicillin.

Drs. Fleming, Florey & Chain (1945) were awarded the Nobel Prize in medicine. They received no money for their amazing discovery.

Therapeutic Decision Making:

- Often a difficult and complex process
- Often confusing and contradictory information
  (Researchers, horse owners, websites & list serve's)
- Frequently our decisions are based on:
  * Our last successful case
  * Our last failure
  * Our last case

Pharmacological Considerations:

- Target
- Mechanism of action
- Route of delivery
- Disposition
- Metabolism/ elimination
- Potential for toxicity

Pharmacokinetics

What the body does to the drug

Describes the movement of drugs in the body

Absorption
Distribution
Metabolism
Elimination

Clinical pharmacokinetics is important for formulating dosage regimens in animals with disease

Pharmacodynamics

What the drug does to the body

Describes the action of the drug on the body- typically related to:
-Plasma/serum concentrations (window into the body)
-Exceptions: Macrolides for respiratory disease & other compounds that are 'tissue-loving'
Values poorly defined in horses- we extrapolate desired 'dose' from human or small animal literature.
Identify the agent;
1. Gram stain (+) (-)
2. disk diffusion test; susceptible,
   intermediate, resistant.
   (based on human serum concentrations)
3. MIC - more expensive but more info.
   resistance often a concentration phenom.
   (minimum concentration of an AB that inhibits
   growth of a pathogen in vitro)

Antibiotic Selection:

Spectrum of Activity (Gram + or Gram -)
Microbial Effect (Cidal or Static)
Bacterial Killing (concentration vs. time dependent)
Post-Antibiotic Effect (aminoglycosides and fluoroquinolones)

Time Dependent drugs

Concentrations need to be above MIC in the body for prolonged period…
Beta-lactams
Sulfonamides

Concentration dependent drugs

High peak concentrations associated with > clinical efficacy
Aminoglycosides
Tetracyclines
Fluoroquinolones

Interval Considerations

- Optimum dose interval = sum of "time required for most effective kill" + "duration of PAE's"
- No method for calculating optimum interval
- Duration of therapy
- Too short = therapeutic failure
- Too long = increase risk of adverse drug events and increase resistance in bacterial population
- "Treat 3 days past the end of clinical signs"
- Clinician experience & accepted practice

"Getting the drug into the horse??"

- Oral administration- many challenges…
- Absorption & tissue distribution determined by drug & species factors (most information defined in humans).
- Generally not ideal in horses
- Drug solubility; gastric pH, particle size, fluid volumes, feed in the stomach etc…

Reasons for Therapeutic Failure

- Wrong diagnosis
- Wrong drug for infection
- Mixed infection
- Resistant strain of bacteria
- Incorrect dosage
- Noncompliance w/ prescribed regimen
- Drug-Drug interaction
- Concurrent underlying disease
- Drug toxicity or adverse effect
- Immune suppression
- Inadequate duration of therapy

Beta-lactam antibiotics

- Penicillin- Procaine penicillin G, Na or K penicillin
- Synthetic penicillins- ampicillin, amoxicillin, ticarcillin
- Cephalosporins-
  - First generation- cefazolin, cephalexin

- Third generation- ceftiofur, ceftazidime
- Fourth generation- cefepime
  - o all have extended gm (-) activity
  - o increased resistance to B-lactamase org.

- Most infections in horses caused by B-hemolytic *streptococcus* spp. (uniformly susceptible to penicillins).
- Primary cephalosporin administered to horses is ceftiofur.
- Advantages include broad spectrum of activity and good safety profile.
- Several studies have evaluated concentrations (lungs, plasma) and safety of ceftiofur over wide range (1.1mg/kg to 11mg/kg) IM and IV.

Ceftiofur

- Approved for use in horses for respiratory tract infections (2.2 to 4.4 mg/kg Q24 IM).
- Higher doses recommended for treating gram - pathogens (Klebsiella,Salmonella,Enterobacter).
- Important to maintain concentrations above MIC with gm (-).
- Unlike other cephlosporins- it is extensively metabolized (desfuroylcetiofur DFC)- primarily excreted in urine
- Protein bound DFC is reservoir for active drug at site of infection (reduced dosing interval)
- Protein binding extends effective half-life (t ½)
- Pharmacokinetic profile; IV vs. IM vs. SQ
- 99% protein bound (clinically significant)
- Binds to acute phase proteins (α1-anti-trypsin) which carries bound drug to sites of inflammation
- Time dependent antimicrobial
- Label dose is 2.2 to 4.4 mg/kg q 24h IM.
- Higher doses (5-10 mg/kg) q 12h IV or IM clinically successful in treating septicemic neonates.
- The IM route of administration + lack of "penicillin rxn's" + broad spectrum of activity = excellent utility in treating polymicrobic infections (pleuropneumonia)

Excede

- Recent FDA approval (ceftiofur crystalline free acid)- sustained-release formulation of ceftiofur in United States
- Indicated for treatment of LRT disease caused by *Streptococcus zooepidemicus.*
- Produces 10 days of therapeutic ceftiofur blood concentrations with 2 IM injections (6.6mg/kg)
- Helps overcome irregular compliance increasing the likelihood of treatment success

Oral B-lactams?

- Very poor absorption and bioavailability
- 2 recent studies in foals; cephalexin and cephadroxil dosed at 30mg/kg PO q 12 hrs was effective

Trimethoprim-Sulfonamide (TMS)

- Considered bactericidal at high concentrations.
- Lipophylic and penetrates tissues well (including central nervous system).
- Broad-spectrum coverage (gm (+), (-) and some anaerobes.
- Interfere with synthesis of folic acid from PABA with sulfonamides competitively inhibiting PABA.
- Purulent fluids rich in protein and PABA, this will decrease TMS activity.
- Good activity against many *Streptococcus* organisms although some resistance noted despite susceptibility results.
- Potentiated sulfas Not recommended for initial treatment of Streptococcus equi infections; [Verheyen K, Newton J et al Equine Vet J. 2000; 32. 527-532].

- Excellent GI absorption although reduced substantially by feeding….(delay feeding).
- Lack of clinical activity against anaerobes.

Trimethoprim-Sulfonamide
- Oral formulation containing TMP with sulfadiazine in a 1:5 ratio commonly dosed at 20 to 30mg/kg BID.
- In horses- rapid elimination of TMP leads to >persistence of sulfonamide and changes optimal ratio. Therefore, potentiated sulfonamides should be dosed BID.
- t½ =sulfamethoxazole 3.5-5 hrs.
- t½ =sulfadiazine 3-4 hrs.
- t½ =trimethoprim 2-3 hrs.
- BID *per os* dosing is necessary to attain therapeutic plasma concentrations of trimethoprim (Dowling in Bertone,2004)

Macrolides

Erythromycin
- Macrolide; bacteriostatic except at high dosages they are -cidal.; good tissue distribution.
- Good activity Strep. Staph. Bacteroides, & Rhodococcus.
- Poor activity E.coli, Pseudomonas, Klebsiella & Salmonella.
- R. equi pneumonia- 25mg/kg q 6-8 hrs will achieve plasma conc. which exceed MIC.

Azithromycin
- Pharmacokinetic advance in macrolide arena.
- High oral bioavailability, large Vd (18.6L/kg) and peritoneal = synovial = serum conc., T1/2 = 20hrs, conc. in bronchoalveolar cells 15- 170x [serum].
- Impression; fewer GI issues.
- Dose;10 mg/kg QD for 5 days then q 48hrs per os.
- Significant advantage over erythromycin.
- Bioavailability =56% in 6 healthy foals
- 10mg/kg QD PO for 5 days then reduced to every other day

Clarithromycin
- Oral bioavailability =57.3% +/- 12.0%
- 7.5 mg/kg BID PO provides serum, pulmonary epithelial lining and bronchalveolar cells of foals above MIC for R. equi isolates during entire 12 hr period
- Determined in 6 healthy foals
- (Womble, 2006)

Rifampin
- Bioavailability is 40 – 70%, lower bioavailability if fed with feed
- t½ =17 hrs. in foals, 6-8 hrs. in adults
- Dose 5mg/kg BID PO
- Emerging resistance especially if used as a monotherapy (Takai, 1997)

Tetracyclines
- Broad-spectrum bacteriostatic activity.
- Excellent tissue penetration (including CNS).
- High GI conc. which may cause diarrhea.
- Effective against several organisms (N.risticii) & Borrelia; oxytetracycline; 5-10mg/kg q 12-24 hrs iv

Doxycycline
- Semi-synthetic tetracycline.

- Very limited bioavailability (+/- 5%), t1/2 = 10-12 hrs.
- CNS penetration and good gm(+) activity.
- Dose; 10 mg/kg BID *per os*

Minocycline
- Semi-synthetic tetracycline.
- Good bioavailability (+/- 25%), t1/2 = 13 hrs.
- CNS penetration and good gm(+) activity.
- Dose; 4 mg/kg BID *per os*

Chloramphenicol
Bacteriostatic (-cidal at high conc.)
- Broad spectrum activity; gm(-), (+) & anaerobes.
- Good intracellular penetration.
- Rapidly metabolized by the liver (short t1/2).
- Oral administration (very bitter).
- Minimize human exposure (animal toxicity rare).
- Dosage25-50mg/kgq4to6hrs*per*

Fluoroquinolones
- Very active against enteric gm(-) and many aerobic gm(+). No anaerobic activity.
- Enrofloxacin- good bioavailability and tissue penetration (higher conc. in resp. tract than serum).
- Arthropathies are concern in foals-not substantiated in adult horses.
- Injectable- 2.5 to 5mg/kg Q24, *per os*- 7.5 to 10mg/kg Q24 is recommended.

Aminoglycosides (General)
- Widely used for treatment of gram (-) infections
- Concentration dependent antibiotics
- If a q24 h approach to dosing is employed, it should be augmented with another AB with gm(+) activity (ampicillin, ceftiofur).
- Serum aminoglycoside assays available at human & vet hospitals.
- Due to individual variability & alterations from disease states, therapeutic monitoring should be employed to optimize dose & interval.

Amikacin
- Concentration dependent aminoglycoside
- Once daily dosing is safer than more frequent administration while being as effective
- Dose 10mg/kg Q24 in adult horses
- Dose 25mg/kg in foals (Papich, 2005)

Gentamicin sulfate
- Rapid, bactericidal action indicated for acute gram (-) infection
- May be administered IM, SQ and IV.
- Synergistic with Beta lactam antibiotics (ampicillin, ceftiofur).
- Do Not administer to horses with compromised renal function
- Dose 6 to 8 mg/kg IM or IV Q24 in adult horses.

Metronidazole
- Nitroimidazole anti-infective- selectively taken up by anaerobes
- Effective vs. anaerobic (Clostridium spp) bacteria and protozoa (Giardia and Trichomonas spp.)

- Vd= 1-2 l/kg
- t½= 3-4 hrs.
- Concentration dependent antimicrobial
- Dose 15-20 mg/kg TID PO
- Widely used for colitis
- Resistance reported (rare) for C.difficile isolates
- Less information available for C.perfringens
- Neonates- 10mg/kg PO q 8-12 hours
- PK profile- Per Os > IV
- Pleuropneumonia PK; 15mg/kg initially followed by 7.5mg/kg PO q6h

Polymyxin B

- Cationic detergent AB (gram -) binds to cell membrane making it more permeable
- PMB was found to decrease in vivo endotoxin-induced TNF activity
- Compared with baseline values 5,000 U of PBM/kg should inhibit 75% of endotoxin induced TNF activity for 12 hours (Parviainen, 2001)