

PHARMACOKINETICS AND PHARMACODYNAMICS



BASICS

OVERVIEW

- The principles of pharmacokinetics and pharmacodynamics relate to drug concentrations at the site of action with the goal of a clinical cure.
- These principles are perhaps best illustrated by examination of veterinary antibiotics and consider bovine respiratory disease as a model these concepts are easier to grasp.
- The dose administered is THE single most important factor relating to a successful clinical outcome under the direct influence of the veterinarian.
- The dose administered is fundamental to all mathematical equations and to the amount of drug at the site of action/infection.

DEFINITIONS

Pharmacokinetics

Pharmacokinetics is a numerical description of all of the processes that occur to a drug between administration and the time that drug reaching the site of action/infection.

- It involves the absorption, distribution, metabolism and elimination (ADME) of the drug.
- This requires measurement of the drug in the body/plasma using rates and concentrations
- Often these data are demonstrated using a serum concentration versus time graphical representation.
- Example pharmacokinetic parameters:
 - Concentration maximum (C_{max})
 - the maximum concentration measured in the serum following drug administration.
 - Time to reach maximum concentration (T_{max})
 - the time between administration of the drug and when the drug reaches the maximum serum concentration.
 - Volume of distribution (V_d)
 - the theoretical volume in which the drug is equally dissolved.
 - Area under the curve (AUC)
 - the mathematical calculation of the area under the serum concentration versus time graph.
 - Half-life (t_{1/2})
 - the time required to clear the body (plasma) of 50% of the drug

If we think of these parameters relative to our model of antimicrobials and bovine respiratory disease, pharmacokinetics represents “what the body does to the drug”.

Pharmacodynamics

Pharmacodynamics is the integration of the pharmacokinetic parameters (drug concentration) and relating this to the amount of drug required for a desired effect.

- It involves the interaction of the drug with its specific cellular or biochemical target (protein receptor, enzyme)
- The processes of pharmacodynamics involve the drug mechanism(s) of action, therapeutic effects and side effects.
- A key principle is that the amount of drug at the receptor site is related to response.

Antibiotic-specific pharmacodynamics

- For antibiotics, the pharmacodynamics parameters relate to the drugs ability to inhibit growth or kill specific bacterial.
- The most common of these is the Minimum Inhibitory Concentration (MIC) for specific bacteria.
 - the MIC is the lowest dilution of an antibiotic that is required to prevent visible growth of the suspect bacteria after incubation in media overnight
 - the MIC test is an in vitro evaluation of the potency of the antimicrobial
- There are several different mechanism of action of veterinary antibiotics
 - inhibit cell wall biosynthesis
 - inhibit of protein synthesis
 - inhibition of nucleic acid synthesis

Antibiotic-specific pharmacokinetic/pharmacodynamics indices

The combination of pharmacokinetic and pharmacodynamics parameters, these indices combine the drug concentration with the MIC to better describe or quantify the therapeutic effect.

- Example PK/PD indices parameters:
 - Time > MIC
 - the amount of time the serum antibiotic concentration is above the MIC value for the bacteria in question
 - Percent time of dosing interval > MIC (% time > MIC)
 - the proportion of the dosing interval that the serum concentration of antibiotic is above the MIC
 - 24-hour AUC/MIC
 - the area under the curve (24 hours) divided by the MIC value for the bacteria in question
 - AUC/MIC
 - the area under the curve divided by the MIC value for the bacteria in question
 - C_{max}/MIC
 - the maximum serum concentration divided by the MIC value for the bacteria in question
- Antibiotic example:
 - How long is the drug above the MIC for specific bacteria?
 - This is explained by the ratio of the time > MIC pharmacodynamic index
 - An antibiotic is given at the labeled dose.
 - The MIC of this antibiotic against *Pasteurella multocida* is 0.6 micrograms/milliliter.
 - The antibiotic's concentration in the serum remains above 0.6 micrograms/milliliter for 96 hours.
 - The time > MIC = 96 hours.

TIME-DEPENDENT ANTIBIOTICS

- Time-dependent (concentration-independent) antibiotics are represented by
 - β -Lactams (penicillins, cephalosporins)
 - Tetracyclines
 - Macrolides
 - Tilmicosin
 - Florfenicol
- With these classes of antibiotics, the time greater than the MIC is an important pharmacokinetic/pharmacodynamic indices that impacts cure rates
- Time-dependent pharmacodynamic parameters
 - Time > MIC
 - Percent of time of dosing interval > MIC (% time > MIC)
 - 24-hour AUC/MIC
- The longer the serum concentration is above the MIC the more likely a clinical cure.
- The serum concentration of antibiotic must be maintained above the MIC for the majority of the treatment period.
 - This is generally accomplished by following labeled dosing recommendations.
 - Accurate estimate of body weight is essential for proper dosing and expectation of clinical success.
 - In humans it is essential that the macrolides and β -lactams maintain a serum concentration remaining above the MIC for at least 40 to 50% of the dosing interval to achieve a clinical cure.

CONCENTRATION-DEPENDENT ANTIBIOTICS

- With these antibiotics as the dose administered is increased (within the approved guidelines), a greater C_{max} and greater antibacterial effects are achieved.
- Concentration-dependent antibiotics are represented by
 - Fluoroquinolones
 - In vitro with fluoroquinolone antibiotics: Greater bacterial killing is noted as the concentration of antibiotic increases.
 - Most fluoroquinolones require a minimum C_{max}/MIC ratio of at least 8 and typically 10 to 12 to effect a clinical cure.
 - This is easily achieved with the labeled dosages for enrofloxacin.
 - Aminoglycosides
 - Florfenicol: Does not appear to require the multiples of MIC to achieve an antibacterial effect against the pathogens of BRD.
- Concentration-dependent pharmacokinetic/pharmacodynamic indices
 - C_{max}/MIC ratio
 - AUC/MIC ratio
- Alternatively, these types of antibiotics can be provided more frequently to achieve more peaks during the treatment period.

PHARMACOKINETICS/ PHARMACODYNAMICS AND CLINICAL CURE

From the Human Literature (Laboratory and Clinical Studies)

- Maintenance of appropriate serum concentration of antibiotic is essential for a clinical cure.
- The dose administered is a crucial component of the concentration at the infection site.
- For concentration-dependent antibiotics: human studies
 - Fluoroquinolones
 - Target the C_{max}/MIC ratio greater than 8

- Target AUC/MIC ratio greater than 100, ideally greater than 125
- For time-dependent antibiotics: human studies
 - Tetracyclines and beta-lactams
 - Serum concentrations of antibiotic must be maintained at concentrations greater than MIC of the causative bacteria for the majority of the dosing interval



MISCELLANEOUS

ASSOCIATED CONDITIONS

From the Veterinary Literature (Laboratory and Clinical Studies)

A possible limitation of the initial Pharmacokinetic/Pharmacodynamic information generated for veterinary antimicrobials is the patient population.

- The primary population for PK studies are healthy animals even though the drug (antimicrobial) will be used to treat a diseased population (bovine respiratory disease)
- The physiologic alterations associated with clinical disease and associated inflammatory/immune response is often unknown.

Additional research and evaluation of drugs in special populations of animals may be required to better understand the role of disease on pharmacokinetic and pharmacodynamics parameters. Some elements that can impact pharmacokinetic parameters:

- age
- production status
- concurrent metabolic disease
- body condition
- Infectious disease and/or associated inflammation

Bovine respiratory disease is a very common infectious disease syndrome of cattle. This economically important syndrome is multifactorial and impacts all ages of animals.

Examples for the impact of bovine respiratory disease of pharmacokinetic/pharmacodynamics parameters

- In an experimental *P. multocida* infection experiment, the concentrations of florfenicol in tracheobronchial secretions of diseased cattle were higher than in the concretion of the secretions of the healthy controls.
- Increased clearance and increased area under the curve for cattle treated with gamithromycin as compared to healthy animals.
- Mastitis is an example of a disease that induces physical and chemical changes to mammary tissues and the milk that can possibly change the ADME of drugs in the mammary glands
- Compared to healthy animals, clinical mastitis in cattle showed differences in pharmacokinetic parameters
 - norfloxacin-treated cows exhibited reduced the half-life, mean residence time and AUC
 - flunixin treated cows, showed reduced the clearance and increased AUC

- ceftiofur hydrochloride treated cows had shorter plasma half-life, higher initial peak concentrations, higher volume of distribution and drug clearance rates.
- These may lead to reduced clinical efficacy and an increased risk of violative residues as compared to the use of these drugs in healthy animals

Dose

- The administered dose is critically important for serum concentration of drug
- The dose is at the center of all pharmacokinetic measurement and key to the effects of the antimicrobial in effecting a clinical cure.
- Sub-therapeutic dosing of drug
 - Decreases likelihood of clinical cure
 - increases the duration of therapy
 - Increases the opportunity for antimicrobial resistance
- Dose is a critical factor that is under control or influence of the medical professional.
 - Ensure clients understand and use the recommended dose of antimicrobials
 - When treating groups of animals, the “pay weight” or “average weight” probably will not accurately dose the entire group
 - body weight variation among the group of animals
 - a portion will be accurately dosed accurately but a percentage will be overdosed and another percentage will be underdosed.
 - increased failure rates for a treatment program may be a dosing issue
 - Look at each animal and adjust the dose to the correct weight if necessary

AGE-RELATED FACTORS

- Age can affect the pharmacokinetics parameters of a specific drug.
- When comparing younger ruminants (<6 months) to adults some differences in PK parameters of ruminants are noted
 - prolonged clearance of most antimicrobials due to underdeveloped hepatic metabolism and/or urinary elimination
 - decreased gastrointestinal (oral) absorption of drugs
 - increased absorption of drugs from intramuscular injection due to the higher percentage of interstitial water in neonates
 - possible increased volume of distribution for water soluble drugs due to greater body water of younger animals
- possible decreased volume of distribution of lipid soluble compounds as neonates have a lower percentage of body fat that increases with age Some of these pharmacokinetic differences are important that may warrant consideration of a dose adjustment
- Often difficult to find pharmacokinetic/pharmacodynamics information for younger animals

PREGNANCY

There are limited studies of pregnant ruminants with regard to PK/PD.

Pregnancy and lactation can significantly alter the pharmacokinetics of specific drugs.

These changes are species and drug specific.

Some of these changes may include:

- increased plasma volume with decreased volume of distribution (Vd)
- decreased plasma albumin with increased free (unbound) drug

Even with a significant PK/PD change because of pregnancy or lactation a dose alteration may not be required.

RESOURCES

Excellent resources that the busy veterinarian may use to quickly find information to consider a treatment protocol for a specific group or population of animals as well as withdrawal times

- Plumb's Veterinary Drug Handbook (see suggested readings).
- Veterinary Drug Monographs housed at AAPVT (see suggested readings)
- Food Animal Residue Avoidance Database (FARAD) (<http://www.farad.org/>) is an excellent resource for information about guidelines for extralabel use.
 - For all of these resources look up the drug by generic name (e.g. florfenicol for Nuflor®) to find information
- Consult the technical services department of the drug manufacturer for questions about special populations.

SEE ALSO

- Food Animal Residue Avoidance Databank (FARAD) (www.fiveminutevet.com/ruminant)
- Common Pharmacologic Therapies: Adult Dairy Cattle (www.fiveminutevet.com/ruminant)
- Extra-label Drug Use and Compounding (www.fiveminutevet.com/ruminant)

ABBREVIATIONS

- AUC = area under the curve
- ADME = absorption, distribution, metabolism and elimination (ADME) of the drug.
- C_{max} = Concentration maximum
- MIC = mean inhibitory concentration
- PK = pharmacokinetics
- PD = pharmacodynamics
- T_{max} = Time to reach maximum concentration
- V_d = Volume of distribution

Suggested Reading

- Craig, W.A. 2001. Does the dose matter? CID 33(Suppl 3) S233–S237.
- Gips, M. and Soback, S. 1999. Norfloxacin pharmacokinetics in lactating cows with sub-clinical and clinical mastitis. J of Vet Pharm and Therapeutics, 22: 202–208.
- Gorden, P.J. Kleinhenz, M.D. Wulf, L.W. et al. 2016. Altered plasma pharmacokinetics of ceftiofur hydrochloride in cows affected with severe clinical mastitis. 99(1):505-14.
- Kissell, L.W. Leavens, T.L. Baynes, R.E. et al. 2015. Comparison of pharmacokinetics and milk elimination of flunixin in healthy cows and cows with mastitis. J Am Vet Med Assoc. 246(1):118-25.

- Modric, S., Martinez, M. Patient variation in veterinary medicine – Part II – Influence of physiological variables. *J. vet. Pharmacol. Therap.* 34, 209–223.
- Plumb, D.C. In: *Plumb's® Veterinary Drug Handbook: 8th Edition*. Wiley-Blackwell, 2015)
- Ramadan, A., Abd El-Aty, A.M. 2011. Pharmacokinetics and Distribution of Florfenicol in Bronchial Secretions of Healthy and *Pasteurella multocida* Infected Calves. *Pharm Anal Acta* 2: 117.doi:10.4172/2153-2435.1000117
- Rotschafer, J.C. Zabinski, R.A. Walker, K.J. 1992. Pharmacodynamic factors of antimicrobial efficacy. *Pharmacotherapy* 12(6 Pt 2):64S–70S.
- Schentag, J.J., Gilliland, K.K., Palandino, J.A. 2001. What have we learned from pharmacokinetic and pharmacodynamic theories? *CID* 32(Suppl 1):S39–S46.
- Slavik, R.S., Jewesson, P.J. 2003. Selecting antibacterials for outpatient parenteral antimicrobial therapy: pharmacokinetic-pharmacodynamic considerations. *Clin Pharmacokinet* 42(9):793–817.
- Veterinary Drug Monographs. Viewed at the American Academy of Veterinary Pharmacology and Therapeutics website. <http://www.aavpt.org/?48>
- Wright, D.H. Brown, G.H. Peterson, M.L., et al. 2000. Application of fluoroquinolone pharmacodynamics. *J Antimicrob Chemother* 46:669–683.

Author Joe Roder

Consulting Editor Christopher C.L. Chase