The Veterinary Antimicrobial Decision Support (VADS) System: Progress and Challenges

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Abstract

This update summarizes progress specifically related to pharmacokinetic dataset categorization and clinical trial literature evaluation as well as challenges encountered in content development. The number of reference datasets available for regimen construction are constantly changing due to new data additions, but currently approximately 164 cattle datasets and 47 swine datasets are the basis for pharmacokinetic projections. Additional datasets are undergoing analysis for small ruminants and poultry. Pharmacokinetic datasets are categorized by animal species, age and health status as well as drug, drug form and injection site. Clinical trial literature is also being accumulated, evaluated and prepared for presentation on the VADS System website. As of the writing of this proceedings article, the VADS System development group is focusing on completing modeling of pharmacokinetic data and entering output on the website in the form of antimicrobial drug regimens combined with pathogen susceptibility profiles. The site is being constructed for ease of long-term maintenance in the form of modification of analysis techniques, addition of new data, and quality assurance of both data entry and data analysis. Data sources and analytical protocols are presented so as to be completely transparent to the user.

Pharmacokinetic Dataset Selection

The Veterinary Antimicrobial Decision Support (VADS) System development continues utilizing procedures as previously reported.[1] Project collaborators include Dr. Mike Apley (Iowa State University College of Veterinary Medicine), Dr. Virginia Fajt (Pueblo, CO), Dr. Cory Langston (Mississippi State University College of Veterinary Medicine), and Dr. Jeff Wilcke (Virginia-Maryland Regional College of Veterinary Medicine). Selection status of literature references and individual datasets are summarized in Table 1 for cattle and Table 2 for swine. These tables report the total number of articles eligible for review and the number of datasets extracted from these articles for use in the VADS System. A dataset is defined as either individual animal timepoint concentration data for multiple animals, mean timepoint concentration data with variance estimates, or pharmacokinetic parameter data with variance estimates that are sufficient for calculation of concentration values at steady state.

In Tables 1 and 2, datasets are classified as having either available timepoint concentration data or pharmacokinetic model parameters. Similar processes have been carried out for small ruminants and poultry. In the VADS System, we are looking for datasets that are capable of standing alone for generating an estimated dose-concentration relationship for inclusion in a linear regression of multiple dose-concentration relationships. These dataset requirements preclude utilizing references with incomplete information. Therefore, Tables 1 and 2 reflect the relatively small number of qualifying datasets obtained from a much larger number of reviewed articles. A single paper may provide multiple datasets due to varying dosing regimens as well as different animal ages or classifications. In the best-case scenario, datasets are obtained for multiple regimens in a drug/species classification. In addition, there are multiple, incompletely reported datasets that are classified as "supporting" data. In some cases, the author of a paper has supplied us with the raw concentration data upon request.

Table 3 includes characteristics of datasets related to intramuscular procaine penicillin G (IM PPG) in cattle. Note that four datasets are obtained from one reference, for which the number of animals per dataset is low. The IM PPG datasets are fairly consistent in injection site, assay type and age of animal while also providing a wide range of dosing regimens.

Table 4 reports characteristics of datasets related to intramuscular ampicillin trihydrate (IM AT) in cattle. All datasets are from separate references and are from the same age category. However, one of the datasets is from cattle with arthritis. The reconstituted suspension concentrations are either not reported or vary widely. We anticipate this to have an effect on the pharmacokinetics determined from each study.

Table 1. Pharmacokinetic datasets undergoing analysis for cattle.

Drug	Articles reviewed	Route	Serum or plasma concentration data	Serum or plasma model parameters
Amikacin	5	IV	°	2
		IM	°	1
Amoxicillin sodium	3	IV	2	°
Amoxicillin trihydrate	12	oral	1 (single dose gavage)	1 (single dose gavage)
		IM	2	2
		SC	1	°
Ampicillin sodium	8	oral	2 (in milk replacer)	1
		IV	1	2
		IM	1	°
Ampicillin trihydrate	12	SC	2	°
		IM	6	°
		oral	°	1 single dose gavage, 1 milk replacer
Ceftiofur sodium	24	IV	6	1
		SC	°	1
		IM	5	1
Chlortetracycline	12	oral	2 (milk replacer)	°
Doxycycline	6	IV	1	2
		oral	°	1 (single dose gavage)
Erythromycin	16	IV	°	4
Florfenicol	18	IV	°	3
		IM	°	2
		oral	°	1 (single dose gavage)
Gentamicin	27	IV	2	6
		IM	6	1
Lincomycin	6	IM	°	1
		IV	°	1
Neomycin	20	IV	1	3
		IM	2	1
		SC	1	°
Oxytetracycline 100 mg/ml	69	IM	8	2
		SC	2	°
Oxytetracycline 200 mg/ml		IM	3	1
Oxytetracycline		oral	2 in milk replacer, 1 single dose gavage	1 (milk replacer)
Oxytetracycline (100/200 mg/ml)		IV	15	11
Penicillin V	1	oral	°	1 (single dose gavage)
Penicillin G potassium	14	oral	1 (single dose gavage)	°
		IV	1	2
Penicillin G procaine	58	IM	6	°
		SC	2	°
		oral	1 (single dose gavage)	°
Penicillin G Benzathine/Procaine	4	IM	1	°
		SC	1	°
Spectinomycin	5	IV	°	1
Sulfadimethoxine	5	IV	2	1
Tetracycline	11	oral	1 (in milk replacer)	°
Tilmicosin	8	SC	3	°
TMP/sulfadiazine	7	SC	1	1
		oral	°	1
Tylosin	17	IV	°	6
		SC	2	°
		IM	3	°

Table 2. Pharmacokinetic datasets undergoing analysis for swine.

Drug	Articles reviewed	Route	Serum or plasma concentration data	Serum or plasma model parameters
Amoxicillin sodium	4	IV	°	3
Amoxicillin sodium		IM	°	1
Amoxicillin trihydrate	6	IM	°	1
Amoxicillin trihydrate		oral	1 through water, 1 single dose gavage	1 (single dose gavage)
Ampicillin sodium	3	IM	1	°
Ampicillin sodium		IV	°	1
Ampicillin trihydrate	3	oral	1 (single dose gavage)	°
Ceftiofur sodium	6	IM	1	°
Chlortetracycline	15	oral	1 in feed, 1 single dose gavage	°
Doxycycline	6	oral	1 (in water)	1 (single dose gavage)
Erythromycin	3	IV	°	1
Florfenicol	1	oral	1 in feed	°
Florfenicol		IM	°	1
Gentamicin	10	IV	°	2
Lincomycin	4	oral	1 (in feed)	°
Oxytetracycline	31	oral	°	3 (all in feed)
Oxytetracycline 100 mg/ml		IM	2	1
Oxytetracycline 100 mg/ml		IV	°	1
Oxytetracycline 200 mg/ml		IM	2	1
Penicillin G Procaine	5	IM	2	°
Potassium Penicillin G	4	IM	1	1
Potassium Penicillin G		IV	°	1
Sulfadimethoxine	13	oral	1 (through water)	2 (single dose gavage)
Sulfadimethoxine		IV	2	°
Tetracycline	3	oral	1 in water, 2 in feed	1 (single dose gavage)
TMP/sulfadiazine	3	oral	°	1 single dose gavage and 1 in feed
TMP/sulfamethoxazole	3	oral	°	1
Tylosin	9	IM	1	°

These differences bring forth the issue of how much to split up datasets according to differences in these categories. It is clear from Tables 1 and 2 that, if the references are categorized into every possible category listed in Tables 3 and 4, there will be many applications with only one dataset per application (e.g., drug x in adult cattle with metritis). Datasets being modeled for inclusion in the VADS System are classified according to the following criteria.

- Drug
- Drug form (e.g., ampicillin sodium, ampicillin trihydrate)
- Animal species
- Animal age
- Animal health status
- Administration route

The current approach is to evaluate different datasets for a drug/route/species combination and exclude ones from a general analysis only if clearly different from the main body of data. One major category for evaluation is healthy versus diseased data.

Concurrent Clinical Trial Data

It is our intent that the user of the VADS System will be able to search for relevant published clinical trials relating to animal species/disease/pathogen/drug

Table 3. Dataset description for intramuscular procaine penicillin G in cattle.

Ref/Dataset	N	Age, Status	Assay Type	Injection Site	Dose (IU/kg)	Suspension Concentration
259[a]	2	Juvenile, Healthy	Bioassay/ cylinder plate	Neck/ dorsal cervical	4,400	300,000 IU/ml
260[a]	2	Juvenile, Healthy	Bioassay/ cylinder plate	Neck/ dorsal cervical	13,200	300,000 IU/ml
264[b]	3	Adult, Healthy	Bioassay/ cylinder plate	Round	20,000	300,000 IU/ml
261[a]	3	Juvenile, Healthy	Bioassay/ cylinder plate	Neck/ dorsal cervical	44,000	300,000 IU/ml
74[c]	6	Juvenile, Healthy	HPLC	Neck/ unspecified	66,000	300,000 IU/ml
263[a]	2	Juvenile, Healthy	Bioassay/ cylinder plate	Neck/ dorsal cervical	132,000	300,000 IU/ml

[a] Hjerpe CA, Routen TA: Practical and theoretical considerations concerning treatment of bacterial pneumonia in feedlot cattle, with special reference to antimicrobic therapy, *Proc Am Assoc Bov Pract* 9:97-140, 1976.
[b] Conlon PD, Butler DG, Burger JP, Gervais MD: Evaluation of route and frequency of administration of three antimicrobial drugs in cattle, *Can Vet J* 34:606-610, 1993.
[c] Papich MG, Korsrud GO, Boison JO, Yates WDG, MacNeil JD, Janzen ED, Cohen RDH, Landry DA: A study of the disposition of procaine penicillin G in feedlot steers following intramuscular and subcutaneous injection, *J Vet Pharm and Therapeutics* 16:317-327, 1993.

Table 4. Dataset description for intramuscular ampicillin trihydrate in cattle.

Dataset	N	Age, Status	Assay Type	Injection Site	Dose (IU/kg)	Suspension Concentration
351[a]	6	Juvenile, Healthy	Bioassay/ cylinder plate	Neck/ dorsal cervical	6.6	Not reported
52[b]	6	Juvenile, Healthy	Bioassay/ agar diffusion	Lateral caudal neck	7.7	200 mg/ml
348[c]	8	Juvenile, arthritis	Bioassay/ agar diffusion	Round	10	250 mg/ml
1944[d]	6	Juvenile, Healthy	Bioassay	Round	11	100 mg/ml
251[e]	6	Juvenile, Healthy	Bioassay/ cylinder plate	Neck/ dorsal cervical	22	Not reported
1926[f]	6	Juvenile, Healthy	HPLC	Neck, lateral	22	250 mg/ml

[a] Hjerpe CA, Routen TA: Practical and theoretical considerations concerning treatment of bacterial pneumonia in feedlot cattle, with special reference to antimicrobic therapy, *Proc Amer Assoc Bov Pract* 9:97-140, 1976.
[b] Nouws JFM, Van Ginneken CAM, Hekman P, Ziv G: Comparative plasma ampicillin levels and bioavailablity of five parenteral ampicillin formulations in ruminant calves, *Vet Quarterly* 4:62-71, 1982.
[c] Brown MP, Mayo MB, Gronwall R: Serum and synovial fluid concentrations of ampicillin trihydrate in calves with suppurative arthritis, *Cornell Vet* 81:137-143, 1991.
[d] Martinez MN, Pedersoli WM, Ravis WR, Jackson JD, Cullison R: Feasibility of interspecies extrapolation in determining the bioequivalence of animal products intended for intramuscular administration, *J Vet Pharm and Therapeutics* 24:125-135, 2001.
[e] Hjerpe CA: A comparison of serum antibiotic concentrations achieved in calves with intratracheal administration of procaine penicillin G, ampicillin trihydrate, tylosin, oxytetracycline hydrochloride, chloramphenicol, chloramphenicol sodium succinate, dihydrostreptomycin sulfate and neomycin sulfate with those achieved with intravenous, intramuscular and subcutaneous administration, *Bov Pract* 14:18-26, 1979.
[f] Apley MD. Publication in preparation.

combinations. Copyright laws will not allow posting of complete references on the website without permission. The maximum outcome data currently available would be an abstract, but may be expanded based on negotiations with copyright holders. Another potential data source may be a link to databases where the article may be purchased electronically. Clinical trial data from the literature is being assembled and evaluated according to the following criteria.

- Drug 1
- Drug 1 regimen
- Additional drugs and regimens as required
- Disease
- Pathogen 1
- Additional pathogens as required
- Animal species
- Animal age
- Type of trial
- Were treatments randomly assigned?
- Were treatment regimens completely described?
- Were assessors of subjective criteria masked?
- Was there a control group?
- Was there a case definition for the disease?
- Were success/failure criteria described?
- Was statistical analysis of data described?
- Were raw data reported?
- Was the infectious organism(s) confirmed?
- Was antimicrobial susceptibility of the infectious organism(s) confirmed?

Conclusions

As of the writing of this proceedings article, the VADS System development group is focusing on completing modeling of pharmacokinetic data and entering output on the website in the form of antimicrobial drug regimens combined with pathogen susceptibility profiles. The site is being constructed for ease of long-term maintenance in the form of modification of analysis techniques, addition of new data and quality assurance of both data entry and data analysis. Data sources and analytical protocols are presented to be completely transparent to the user.

Reference

1. Apley MD: Using the Veterinary Antimicrobial Decision Support (VADS) System to evaluate therapeutic regimens. *Proc Am Assoc Bov Pract* 36:68-72, 2003.