

Practical pharmacology for the field

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Abstract

The use of pharmacokinetics and pharmacodynamics for regimen construction may be useful when clinical data is lacking, but the inputs must be carefully considered for validity. Clinical experience is also useful in determining appropriate therapeutic paths when the multiple components of clinical response are considered in addition to the contribution of the drug. The balancing act of therapeutic intervention is well characterized by a review of the data available to define potential benefits and harm from the use of dexamethasone in cattle. These benefits are poorly defined in the literature in relation to regimens commonly used in practice, while the potential detriments are more clearly defined in relation to adverse reproductive effects, immunosuppression, alteration of treatment efficacy, and the relatively new potential for violative residues when used close to slaughter.

Key words: cattle, pharmacology, therapy, treatment regimen

Résumé

L'utilisation de la pharmacocinétique et de la pharmacodynamique dans la formulation des régimes médicamenteux peut être utile si les données cliniques ne sont pas disponibles tant et aussi longtemps que les entrants soient soigneusement choisis pour leur validité. L'expérience clinique est aussi utile afin de déterminer les voies thérapeutiques appropriées lorsque les multiples composantes de la réponse clinique sont prises en considération en plus de la contribution du médicament. Le constat d'équilibre lors d'une intervention thérapeutique est renforcé par une revue des données disponibles sur les effets bénéfiques et nocifs de l'utilisation de la dexaméthasone chez les bovins. Ces bénéfices ne sont pas bien établis dans la littérature en égard aux régimes couramment utilisés en pratique. Les aspects néfastes sont mieux connus dans le contexte de la reproduction, de la suppression immunitaire, du changement de l'efficacité du traitement et de la possibilité assez récente que des résidus excessifs soient présents lorsque le médicament est utilisé peu avant l'abattage.

Introduction

Clinical pharmacology is about the application of drugs in the field, usually with the detail of interest

at the moment viewed as clinical, with all other detail considered academic or trivial. With this in mind, the following definition of clinical pharmacology boils the subject down to the basics.

1. Can I do any good with this regimen?
2. Can I do any harm with this regimen?
3. Can I get it in the animal?
4. Does the hoped-for outcome justify the cost?

The latter 2 focus on practicality of administration requirements and calculations concerning return on investment (ROI). The first 2 allow application of principles of clinical pharmacology in your thought process, and are the focus of these proceedings.

Doing Some Good

The therapies we use have more potential to make “a difference” than “the difference”. The physiology-based approach of using pharmacokinetics and pharmacodynamics to predict drug efficacy has some merit in guiding us towards reasonable regimens, but this approach is dependent on several key factors.

- Accurate characterization of pharmacokinetics
- An emphasis is now being put on free drug concentrations as opposed to total drug concentrations, which may include significant portions of bound drug that is unavailable for activity.
- Concentrations may or may not be relevant to clinical efficacy, depending on “concentrating” tendencies with unknown contributions of these concentrations.
- Tissue homogenization and plasma concentrations of macrolides are considered unsatisfactory for comparing to minimal inhibitory concentrations (MICs) of target pathogens for respiratory disease. Pulmonary epithelial lining fluid (PELF) is now being investigated as an indicator concentration.
- Drug concentrations in milk are suspect for comparing to pharmacodynamic indices, because of unknown location and concentration of the drug in relation to the pathogen or tissue site of activity prior to and after milk letdown. Studies reporting milk concentrations of drugs based on periodic milkings are really residue studies.

- Appropriate pharmacodynamic indices
 - Most of the antimicrobial pharmacodynamic indices we use in cattle have been developed for other pathogens in other species, such as a *Staphylococcus aureus* mouse thigh infection model.
 - Or, we run off of pharmacodynamic assumptions based on mechanism of action, as in the first-generation tetracyclines (chlortetracycline, oxytetracycline).
 - There are now indications for some antibiotics that they may change from bactericidal to bacteriostatic as the MIC of the pathogen rises.
 - For drugs such as aspirin, we model based on human plasma target concentrations for pain control. There is some hope, as this target concentration was supported as a reasonable choice for modeling in cattle by Coetzee et al.¹

Physiological reasoning may be useful to initiate clinical trials, or to inform regimen construction when alterations are needed or where clinical data are not available. However, physiological reasoning is always trumped by clinical trial data utilizing negative controls, or a relevant, well characterized positive control. But, clinical observations and examination of treatment records for therapeutic outcome can also inform us as to drug efficacy, correct? How good are you at picking out the actual drug effect from all of the other noise in day-to-day practice? To evaluate the ability of your well-developed observational muscles to discern differences in drug effect based on treatment-outcome data, let's look at a data set outside of bovine medicine and take on an equine example.

Excede (ceftiofur crystalline free acid, Zoetis) has been approved for respiratory disease in horses, with the clinical efficacy studies published in the peer-reviewed literature.² The results were reported for all cases, and

then for the subset of cases which had positive culture results for *Streptococcus equi* subsp *zooepidemicus* (“*Strep zoo*”). Our example focuses on the difference in treatment outcome in the overall group and the *Strep zoo*-positive subset.

The success rate, as defined in this study, was 86% for all treated cases, and 67% for the subset of these treated cases which were positive for *Strep zoo* (Figure 1). The clinical success rate was 19% less in the *Strep zoo*-positive cases than in all cases. The question is, did the drug work less well in the *Strep zoo*-positive cases as opposed to all cases combined (86% vs 67% clinical response rate)? Please make your decision before reading further.

The rest of the story: this was a negative-control clinical trial, and here are the negative control clinical success rates. For all cases, it was 54%, and for the *Strep zoo*-positive subset it was 32% (Figure 2). Now what do you think? Change your answer? Please make a decision before reading ahead.

The answer is that the Attributable Reduction in Risk (ARR, the actual percent difference in clinical success rate between treated and control groups) is 32% for all cases (86% treated success – 54% control success) and 35% in the *Strep zoo* subset (68% treated success – 33% control success). These are basically the same. The difference in overall clinical success was because of the difference in disease challenge as reflected in spontaneous recovery in the control group; the drug made the same difference between treated and controls in both groups. You needed to treat 3 animals in either group to make a difference in 1, (100% divided by the ARR is the Number Needed to Treat [NNT], the number of animals you must treat to make a difference in one animal).

This study illustrates that when evaluating treatment outcomes, the results are a combination of the severity of the disease challenge, the animal response to this challenge, and the drug effect. It is possible to have drastically different therapeutic outcomes in 2

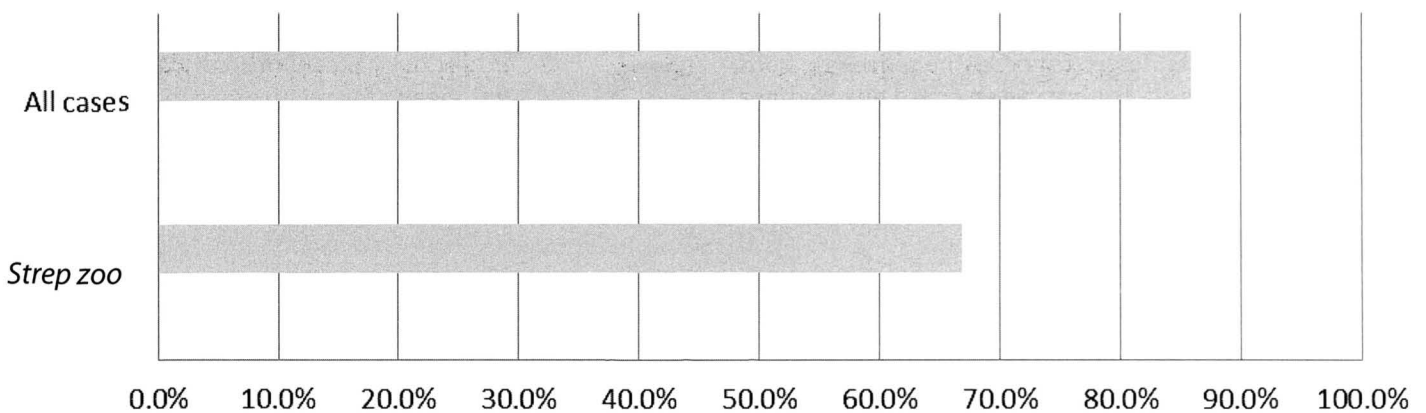


Figure 1. Clinical success rates (%) for horses treated for respiratory disease with ceftiofur crystalline free acid.

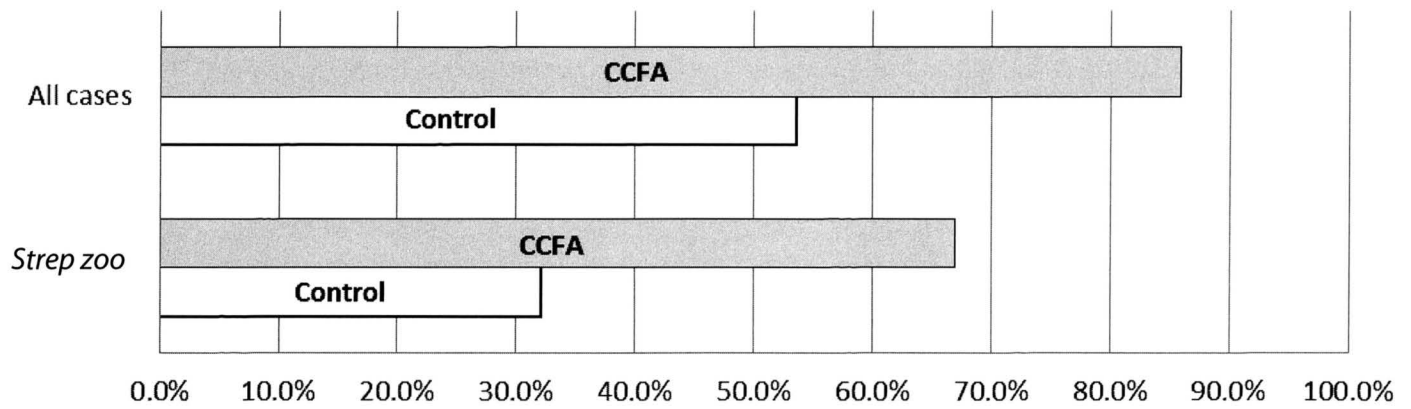


Figure 2. Clinical success rates (%) for horses treated for respiratory disease with CCFA or negative control.

populations with the drug essentially having the same effect. Without knowing the results of contemporaneous negative controls, we are unable to separate the drug effect from the other 2. It takes a negative-controlled clinical trial, or a positive-controlled trial with a very well characterized positive control (recently characterized with negative controls), to tell us the actual benefit we are getting from a drug.

The big question is whether or not a drug is really providing a benefit. With the increased scrutiny placed on drug use in food animal production, it is more important than ever to know if some uses are even worth continuing and defending. Dexamethasone is a good example of looking for evidence of therapeutic effect which leaves us with multiple questions.

For the use of dexamethasone in the treatment of toxic mastitis, I was unable to find a study utilizing naturally occurring disease. Lohuis et al, utilized a model where 30 mg dexamethasone was given intramuscularly to cows immediately following placement of *E. coli* into the mammary gland.³ The formulation consisted of 1 mg dexamethasone sodium phosphate and 2 mg dexamethasone phenylpropionate per ml as a suspension. An antibiotic was not administered until 24 hours later. Dexamethasone-treated cattle had reduced mammary gland swelling, maintained rumen motility, and less reduction in milk production as compared to untreated controls. The treated group had higher rectal temperatures.

Anderson and Hunt used an endotoxin-induced mastitis model to evaluate a dose of 0.2 mg/lb (0.44 mg/kg) administered 2 hours following introducing purified endotoxin into the mammary gland.⁴ At this very high dose, dexamethasone-treated cattle had lower rectal temperatures, increased loss of milk production, and no difference in somatic cell count as compared to untreated controls. For the available mastitis data, we are left wondering about the application of the doses, the formulations used, and the induced models as to how

dexamethasone might be used in practice.

The classic study on using dexamethasone for bovine respiratory disease was published over 35 years ago.⁵ Christie et al utilized intravenous oxytetracycline (5 mg/lb; 11 mg/kg) and pyrilamine (250 mg), with or without 20 mg dexamethasone, daily for 3 days for naturally occurring bovine respiratory disease. Treatment failures received the same treatment until recovery, out to a maximum of 9 days. Treatment response was decreased ($P \leq 0.05$) and relapse rate was increased ($P \leq 0.01$) in dexamethasone-treated cattle. As for mastitis, we are left considering the application of this treatment regimen and potential dexamethasone duration to today's regimens and a single dexamethasone injection. However, we can conclude that a beneficial effect of dexamethasone on bovine respiratory treatment has not been demonstrated.

The efficacy of penicillin G alone or in combination with dexamethasone has been evaluated in naturally occurring infectious bovine keratoconjunctivitis.⁶ The penicillin treatment group (n = 18) received 1 ml (300,000 IU) of procaine penicillin G in the superior subpalpebral conjunctiva once daily for 3 days. The penicillin G/dexamethasone group (n = 13) received penicillin G as for the previous group plus 1 ml (4 mg) of dexamethasone sodium phosphate in the affected eye (different subpalpebral conjunctiva location) once daily for 3 days. The control group was not treated. Treatment was started when an ulcer was observed. There were no significant differences in healing between treatment groups. It is interesting to note that the mean healing time for ulcers was numerically longest for the penicillin G/dexamethasone group.

Doing Some Harm

Dexamethasone again serves as a good example of searching for evidence of harm as demonstrated by

detrimental effects on treatment outcome, harmful side effects, or causing the potential for a violative residue.

The first potential for harm in food animals that comes to mind is the potential for reproductive effects, starting with abortion during the last trimester, retained placenta, and metritis.⁷ Also, the potential effect of dexamethasone on bulls cannot be overlooked. A 1994 study by Barth et al evaluated the effects of both scrotal insulation and dexamethasone administration on semen quality of 2-year-old bulls over a period of 6 weeks.⁸ The study was conducted over 2 summers on bulls previously determined to have adequate semen quality. Nine bulls were used the first summer (1 control, 4 insulated, 4 dexamethasone) and 11 bulls the second summer (3 controls, 4 insulated, 4 dexamethasone). Dexamethasone was administered at 20 mg IM, every 24 hours for 7 days. Semen was collected 3 times a week for the first 25 days after treatment initiation, and then twice weekly through 42 days. Semen was evaluated for volume, concentration, motility, percent alive, and 22 abnormalities.

Dexamethasone-treated bulls had significantly reduced serum testosterone concentrations as compared to pretreatment and to the other treatment groups. Sperm defects varied by bull, but were similar for both treatment groups and were resolved by 42 days post-treatment. Percent dead sperm in dexamethasone bulls went from a pretreatment mean of approximately 25% to peaks of 40-45% during 12-32 days following treatment (data extrapolated from graph). The reduction in testosterone is consistent with previously reported effects of dexamethasone on testosterone concentrations in bulls (decrease noted 4 hours after treatment).⁹ Dexamethasone has also been shown to increase spermatozoa crater defects in bulls.¹⁰

The immunosuppressive effects of dexamethasone in cattle have also been well characterized. Roth and Kaeberle have used dexamethasone at 0.9 ml/100 lbs of a 2 mg/ml solution (0.04 mg/kg) daily for 3 days as a research model to suppress neutrophil function in cattle to allow the evaluation of compounds to reverse this suppression.¹¹ Chiang et al used this same regimen beginning 24 hours after initiating an induced *Histophilus somni* model to demonstrate that the dexamethasone-treated calves had increased extent and severity of pneumonic lesions 7 days after model initiation, and the only mortalities prior to study completion were from the dexamethasone group.¹² In addition, Rock et al demonstrated that a single 1.3 mg/lb (2.8 mg/kg) dose of dexamethasone is capable of reactivation of latent bovine herpesvirus-1 in a rabbit model.¹³

Sreerama et al used dexamethasone immunosuppression as part of a study to demonstrate that dexamethasone-treated calves had higher shedding of an inoculated *E. coli* O157:H7 at days 4 and 7 post-

treatment than control calves.¹⁴ The regimen was 0.11 mg/lb (0.25 mg/kg) intramuscularly per day for 5 days, with inoculation occurring on the third day.

Another new potential for harm with dexamethasone is causing a violative residue. Dexamethasone is labeled as an anti-inflammatory agent in cattle at a dose of 5 to 20 milligrams, with no use class stated or implied.⁷ No withdrawal time is specified on the label, leading to an interpretation of no necessary preslaughter withdrawal time. However, the Food Safety Inspection Service (FSIS) of the US Department of Agriculture has interpreted the lack of a tolerance reported in 21 CFR Part 556 as indicating that any residue detected is violative. Therefore, the FSIS has been reporting any detected dexamethasone residue as violative starting with the introduction of their new multiresidue screening method.¹⁵ Producers and veterinarians first learned of this new interpretation when informed of dexamethasone residue violations. Hopefully, discussions with the Food and Drug Administration Center for Veterinary Medicine will clarify the reason for no tolerance in 21 CFR Part 556, and this issue will be resolved in the near future. In the meantime, the Food Animal Residue Avoidance Databank (FARAD) has suggested withdrawal times for cattle listed under FARAD-recommended withdrawal intervals for extra-label use of approved food-animal drugs.¹⁶

Conclusions

Physiological reasoning in the form of pharmacokinetic/pharmacodynamic reasoning can be very useful for narrowing down reasonable regimens to take into clinical trials, for ruling out entirely unreasonable regimens, and for suggesting reasonable regimens when clinical data is lacking or where regimens need to be altered in the face of declining therapeutic efficacy. However, these evaluations should be conducted with a good understanding of the limitations of the pharmacokinetic and pharmacodynamic information being used. For example, simply matching the most convenient antimicrobial concentration with an MIC is not necessarily a predictor of clinical efficacy.

Clinical trial data trumps physiological reasoning. We need to be careful to recognize the differences in clinical outcome observations and negative-controlled, randomized clinical trials and adjust our interpretations accordingly.

Dexamethasone is an example of a drug where we have little information to support efficacy in clinical use in mastitis, respiratory disease, or pinkeye, and some data to suggest lack of efficacy and even detrimental effects. Shortfalls in the clinical data available are uncertainty in how to relate regimens used to generate these data to regimens used in practice, and how induced

models relate to naturally occurring disease. However, we do have significant evidence for potential harm with dexamethasone, including adverse reproductive effects in both cows and bulls, immunosuppression at prolonged dosing regimens, and the potential for violative residues. These examples highlight the balancing act performed by veterinarians in their daily therapeutic decisions.

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