You can do this: Applying clinical pharmacology in practice

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Abstract

The term "clinical pharmacology" strikes fear in the hearts of many a veterinary graduate, bringing back memories of Socratic questioning in rounds as to the pharmacokinetic and pharmacodynamic interactions leading to a desired drug effect. These were concepts and facts that must have been known only to the reader of an ancient scroll, hand-written in the fading ink of a long-dead language. But take heart! The happy little secret is that all the PK/PD interactions, mechanisms of action, and physiologic reasoning are valuable only if they help to lead us to the promised land of clinical efficacy. As clinical veterinarians, that is what we care about. It turns out that you are the best qualified person to take clinical efficacy data and decide if it applies to your clinical situation. All it takes is a system to evaluate the quality of clinical evidence, an understanding of the concepts involved in a little thing called Number Needed to Treat, and some introspective thinking about our own biases.

Introduction

I think one of the biggest concerns about applying clinical pharmacology in practice is the fear of the unknown unknowns; what is it that we do not know that will cause us to make a bad therapeutic decision? A standard approach to thinking through therapeutic decisions will help. But all these evaluation skills are applied in an environment where even specialists struggle to keep up on the literature in their particular areas, let alone have sufficient time to critically review and consider the internal and external validity of each piece of information. The challenge becomes taking up a position between the 2 opposites of clinical practice as illustrated in Figure 1. The first thing to do is to work through a checklist, creating a standard procedure for approaching a problem. This also works for questioning someone bringing a new product or procedure to your attention.

A checklist for applying evidence to the selection of a therapeutic compound in food animal medicine

Let's start by getting comfortable with evaluating evidence which has the potential to help you understand the difference that will be made in clinical outcome from an application of a drug in an animal or a particular system. Here are some reasonable steps.

1. **How much of the observed clinical response rate is due to the drug and how much is due to spontaneous recovery?** The only way to know is with the appropriate control groups. That is why it is extremely difficult, really impossible, to judge the actual contribution of a drug to clinical outcomes by evaluating treatment records of your clients. Looking back in time prior to a treatment protocol change isn't a great answer; historical controls get us in trouble all the time. There is a huge difference in telling what happened (treatment outcomes) and telling why it happened (how much of the response may be attributed to the drug). That isn't an ivory tower puritanical attitude, it is just fact. We can conjecture as to reasons for treatment outcomes, but we need to be honest with ourselves on the mix of conjecture and fact. See the section on Number Needed to Treat, below.
2. **Is appropriate clinical trial data available to drive my decision process?** Here's how to evaluate data being given to you.
   a. Prospective? (Was the study planned ahead of time and implemented according to this plan?) Retrospective studies with appropriate controls and analysis, such as case control studies, may be informative but nothing beats a good prospective, randomized, masked clinical trial in the right animal population.
   b. Randomized? (Did each experimental unit have an equal chance of being assigned to any of the treatments?) This is an absolute requirement. If you aren't assured of this, just walk away. And don't kid yourself that if doing a quick "study" for yourself you can see through any confounding due to not randomizing.
   c. Masked? (Were any subjective evaluators, as in those assigning clinical scores, unaware of the treatment applied to the animal or group being evaluated?) Another absolute requirement. No, a subjective evaluator cannot also administer treatments. We all think we can control our bias in subjective evaluations; we really can't. As for randomization above, if you aren't assured of masking, just walk away.
   d. Controlled? (Were there appropriate units for comparison, as in positive or negative controls?)

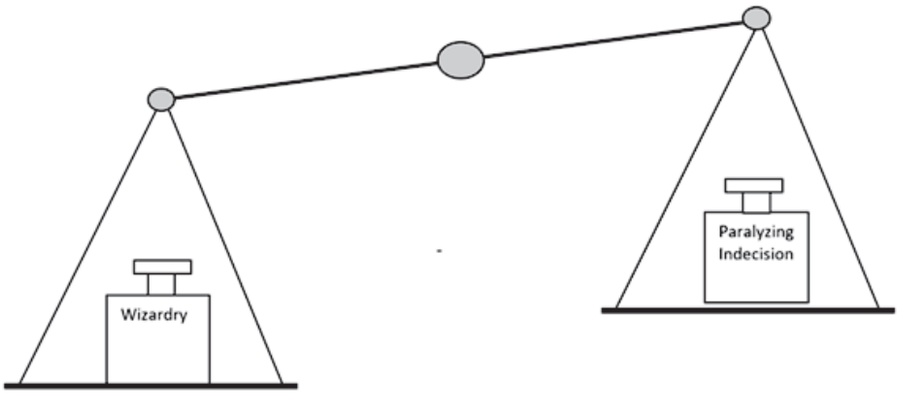

Figure 1. Clinical Experience "Making the same mistakes with increasing confidence over an impressive number of years"

The only way you can really tell what contribution a drug makes to clinical outcome is with the proper negative control group, or a really well characterized positive control. You can tell what happened without the control groups; you just can't make any decisions as to the drug contribution.

e. Appropriate statistical treatment? This stops some people from even trying. If the study makes it over the first hurdles above, and is going to be pivotal in a practice decision, reach out and ask someone. An academic person may be able to help you, or almost all of us know someone who can.
f. Applicable to this production system? Here, you are the expert. Don't let this slip by you.
    i. Animal type and production stage
    ii. Case definitions for illness and success/failure
    iii. Is the regimen practical?
g. Are the trial outcome parameters an actual clinical response or a substitution variable? As a mentor of mine once said, "I've never gone to the supermarket to buy a pound of titers". It also takes a lot of barbeque sauce to fill you up when feasting on some grilled rectal temperature data.
    i. Fever reduction vs change in clinical outcome
    ii Titers vs disease protection

3. **For antimicrobials, do I understand the application of antimicrobial susceptibility testing?** This is a whole other subject with lots of debate about application. I'm convinced it can help, but interpretation goes beyond "S good, R bad". Talk with the microbiologist running the test for you or seek out a clinical pharmacologist to help you sort through the susceptibility testing results. When we get away from CLSI approved breakpoints for diseases in animals, the interpretation becomes a lot more complex and you may end up dealing with more of a wildtype/non-wildtype epidemiological cutoff value situation than a clinical breakpoint.
4. **Is it legal?** Think through the Animal Medicinal Drug Use Clarification Act (AMDUCA) and prohibited drugs for extralabel use in food animals. Keep in mind that a major obligation of a food animal veterinarian is to keep violative residues out of food animal products. The compounding guidelines from the Food and Drug Administration Center for Veterinary Medicine (FDA/CVM) are being reviewed and revised right now, but there are still key guidance points for compounding in the AMDUCA regulations, such as the prohibition on compounding from bulk drugs. If someone refers to a compounded product as a generic, quickly correct them; they are nowhere near the same thing.
5. **Have you thought through the disposition of animals after receiving this drug?** Does the withdrawal time fit with the upcoming or possibly upcoming disposition of the animal? Remember our obligations with extralabel use.

What is the Weight of Evidence Behind a Label Claim?

For recently approved drugs, you can access the label summary and associated Freedom of Information summary (FOI) at the "Animal Drugs @ FDA" site. All you need to do is search the name of this site and up it comes. At this site, you can search by generic or proprietary name of the drug. After clicking on a specific NADA (New Animal Drug Application) approval number, you can look at label inclusions as well as accessing the FOI document for this NADA # and any applicable Blue Bird labels (example labels for feed products, sold by the hypothetical Blue Bird Feed Company, Anytown, USA). The FOI document contains summaries of the data submit-

ted to gain approval of the drug label. The Blue Bird labels are example labels for in-feed drugs which include all the necessary label inclusions for a Type B or Type C medicated feed label. You are also able to determine concurrent feeding clearances by looking through these labels.

Now let's talk about defining just what difference a drug makes in clinical outcome: Attributable Risk Reduction (ARR) and Number Needed to Treat (NNT)

Attributable risk reduction (ARR) refers to the decrease in risk of an adverse event, in this case the decrease in risk due the treatment in question. The adverse event may be continued morbidity, or mortality, in the case of therapy. When the treatment in question is applied in a control or prevention manner, the adverse event may be the occurrence of a clinical case. The ARR is expressed as the actual % difference in response between the treated and control groups.

Number Needed to Treat (NNT) refers to the number of animals to which the treatment must be applied to result in an outcome difference for one animal. It is calculated from the ARR as in the example below.

Example of applying NNT: An antimicrobial treatment is individually applied to calves for therapy of respiratory disease in a study where another group of calves received no treatment for the same clinical presentation. The calves were randomly assigned to either the treatment or negative control group, calf was the experimental unit, and subjective evaluators of treatment outcome were masked to treatment. A clinical success rate of 25% was noted for the untreated control calves (considered to not meet treatment criteria at the time of outcome evaluation and did not need to be treated again during the study) and 75% was noted for the treated calves. The failure rates would therefore be 75% for the controls and 25% for the treated group. The ARR is calculated determining the difference in the rates; if there are only 2 outcome options, you can use either the difference in success or failure rates as the ARR, it comes out the same. In this case, the ARR is 50% (75% - 25% = 50%). To determine the NNT, divide the ARR % value into 100%. In this example, the NNT would be 2 (100 ÷ 50 = 2). You need to treat 2 calves to create a difference in clinical outcome in 1 calf.

When presented these values, you would know from the ARR that there was an actual 50% difference between the failure or success rates. The NNT value converts these to how many calves would need to be treated to make a difference in 1 animal. A more intuitive way of looking at the numbers involves looking at how many success or failures would be present in common in both treatment groups. Since 1 in 4 calves would be a failure (25%) and 1 in 4 calves would be a success (25%) regardless of treatment, that leaves 2 out of 4 calves where the treatment makes a difference. This is equivalent to 1 out of 2 calves, meaning we must treat 2 to see a difference in 1 calf.

The NNT is useful for calculating the economic outcomes of treatment by understanding how many animals must receive the treatment before you make a difference in 1. However, we must understand that this calculation is based on the specific outcome parameter being used. For example, focusing on the treatment success example above fails to incorporate the possible economic benefits of a successfully treated respiratory disease case, such as improved cost of gain and improved carcass quality. It is up to you to consider all the applicable outcome parameters that may surround the one being considered.

We all know we are supposed to consider evidence in our therapeutic decisions, but what is evidence-based medicine?

Therapeutic challenges in daily practice require a decision. If you can only make decisions in the light of clear, well documented evidence, then paralysis will often result because definitive evidence isn't always available. If decisions are usually made based on selective memory and the most recent technology, then you have earned the title of wizard. Practicing between these 2 extremes requires knowing what the complete body of evidence is, which evidence is sufficiently valid to consider, and how this evidence applies to your practice situation. This is a description of evidence-based medicine.

Sackett et al described evidence-based medicine (EBM) as "the integration of best research evidence with clinical expertise and patient values".[3] In veterinary medicine we replace patient values with client values. However, we must also consider the patient in the context of animal welfare and food quality/safety. Hopefully, these are also a major part of our client's values. It is also important to define practices which do not meet the criteria for evidence-based medicine. These would include the following (with input from Dr. Richard Evans):

- Just asking an "expert" (this is the replicating mode)
- Only relying on evidence without including experience
- Not critically appraising the evidence
- Not systematically searching for all the evidence

Supreme Court Justice Potter Stewart unknowingly defined traditional medicine when he reviewed an Ohio decision banning the Louis Malle movie "The Lovers" due to pornographic content. Justice Stewart said, "perhaps I could never succeed in intelligibly defining pornography, but I know it when I see it, and the motion picture involved is this case is not that". Do you "know a good treatment (or management practice) when you see it"? Cockcroft and Holmes have provided further insight into differences between traditional approaches to medicine and EBM as presented in Table 1.[1]

It is irresistible to include some tongue-in-cheek examples of alternatives to evidence-based medicine published by Isaacs and Fitzgerald.[2] In one definition, they also give a rather searing definition of clinical experience.

Table 1. The differences in the traditional approach to medicine and evidence-based medicine. Cockroft and Holmes, 2003.

Traditional approach	Evidence-based approach
"Clinical experience is a valid way of gaining an understanding about diagnosis, prognosis and treatment."	"Personal experience may be misleading"
"Pathophysiological rationale is a valid way of guiding treatments."	"Randomized studies are required to validate results because predictions based upon physiology may be wrong."
"Common sense and classical medical training are the only qualities needed to evaluate medical literature."	"Reading literature requires more than common sense to evaluate the evidence."

"**Eminence-based medicine** – The more senior the colleague, the less importance he or she placed on the need for anything as mundane as evidence. Experience, it seems, is worth any amount of evidence. These colleagues have a touching faith in **clinical experience, which has been defined as "making the same mistakes with increasing confidence over an impressive number of years."** The eminent physician's white hair and balding pate are called the "halo" effect.

Vehemence-based medicine – The substitution of volume for evidence is an effective technique for brow-beating your more timorous colleagues and for convincing relatives of your ability.

Nervousness-based medicine – Fear of litigation is powerful stimulus to over-investigation and over-treatment. In an atmosphere of litigation phobia, the only bad test is the test you didn't think of ordering.

Confidence-based medicine – This is restricted to surgeons."

The pursuit of evidence-based medicine can be frustrating, and the reader is referred to the 5th edition of *Evidence-Based Medicine - How to Practice and Teach EBM*, which has moved on to a new string of authors but covers the same basic content in a short and practical manner. But for now, let's define clinical experience (expertise) in veterinary medicine.

Sackett et al define clinical expertise as "…the ability to use our clinical skills and past experience to rapidly identify each patient's unique health state and diagnosis, their individual risks and benefits of potential interventions, and their personal values and expectations." How much of our clinical experience is based on historical controls, or no controls? In addition, many of our interactions with clients and patients involve no definitive initial diagnosis and lack adequate follow up on the true outcome of the intervention. This paper is not meant to discount valuable experience. However, when we fail to question our own observations, we become authoritarian (opinions-based advice based on prejudice and pride) as opposed to authoritative (evidence-based advice based on appraisal of relevant research).[1]

We have talked about evaluating evidence, but it is helpful to have a ranking system. This is a proposed ranking system from Cockroft and Holmes as adapted by the author and Dr. Richard Evans. It starts with the type of evidence that should be given the most weight.

1. Blinded controlled randomized trials
2. Observational studies
    1. Cohort
    2. Case-control
3. Case series
4. Case report
5. Consensus report
6. Comparative animal research
7. *In vitro*
8. Substitution variables
9. *In silica* (computer modeling)

While not giving definitive guidance, it is at least helpful to have a basic guide to what kind of studies and trials offer the best evidence that may be converted to clinical action.

Conclusions

Hopefully, this presentation gave some basic organization to your evaluation of evidence, and when to decide to, or not to, apply evidence in your practice. Keep putting yourself in situations where you are challenged and are exposed to new evidence and differing opinions. It's all about clinical efficacy in applications which apply to you and your clients. You are the best judge of that.

References

1. Cockroft P, Holmes M. *Handbook of evidence-based veterinary medicine*, 1st ed. Oxford: Blackwell Publishing Ltd., 2003.
2. Isaacs D, Fitzgerald D. Seven alternatives to evidence-based medicine. *Oncologist* 2001;6:390-391.
3. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB, Livingstone C. *Evidence-based medicine: How to practice and teach EBM*. Edinburgh: Churchill Livingstone, 2000.

Notes