The Role of the Clinical Pharmacologist in Animal Health

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Cory Langston¹ and Cyril R. Clarke¹

¹ College of Veterinary Medicine, Box 6100, Mississippi State, MS 39762-6100

ABSTRACT Like most scientific disciplines, pharmacology is replete with subspecialties. Certainly most scientists recognize the value of animal studies in drug development for human pharmaceuticals. However, animals as the target species also represent a major focus of investigation. According to recent estimates, in the United States for the year 2000, 98.1 million cattle, 59.8 million pigs, and 1.5 billion chickens existed. Added to that estimate were companion animals, including 4 million horses, 59 million cats, and 52.9 million dogs^{1,2}. The estimate does not include the so-called "minor" species, such as 7 million sheep and 320 000 acres of freshwater fish production^{1,3}. In most respects, the medical needs of these animals are addressed in a manner parallel to that of human medicine. One such parallel, with certain distinct differences from its human counterpart, is veterinary clinical pharmacology.

KEYWORDS: veterinary clinical, pharmacology, species differences, academia, industry, regulatory.

THE NEED FOR VETERINARY CLINICAL PHARMACOLOGY In 1937, Harry Gold described the need for the interface between pharmacology and clinical medicine that we now call clinical pharmacology. He recognized that the physician directing patient care too often did not consider pertinent points of basic pharmacology and proper drug use. If this is true for human medicine, it is an even greater issue in veterinary medicine for a number of reasons.

A primary variable that must be accounted for in veterinary clinical pharmacology is that of species differences in drug behavior. While the physician may be familiar with the saying that "children are not small adults," it is even more appropriate to note that "cats are not small dogs," "sheep are not small cows," and so on. Many such disparities are based on pharmacokinetic differences (eg, the elimination half-life of salicylate is 27 to 45 hours in the cat, 4.5 to 8.5 hours in the dog, and 0.5 hours in the cow). Accordingly, the dosages for these species are quite different, ranging from 10 to 20 mg/kg orally every 2 to 3 days in the cat, 10 to 20 mg/kg orally

every 12 hours in the dog, and 100 mg/kg orally every 12 hours in the cow.

The reasons for this kinetic dissimilarity include metabolic differences (cats are deficient in glucuronyl transferase) and basic physiologic differences. For example, compared to carnivores, cattle have alkaline urine and therefore ion trap weak acids. Anatomical differences also play a role in kinetic dissimilarities, particularly with respect to gastrointestinal absorption characteristics. Again, using aspirin as an example, horses have only a slightly longer elimination half-life (1 hour) versus the cow (one-half hour); however, the drug is practically useless as an analgesic and antipyretic in the former yet quite effective in the latter. Specifically, because the horse is a monogastric, the drug is rapidly absorbed following oral administration but likewise removed rapidly due to its short elimination half-life. As such, an aspirin dosage in the horse of 35 mg/kg orally every 2 hours would be necessary to maintain effective concentrations while avoiding toxicity. Such a dosing regimen is logistically impractical. While one might assume that the recommended 100-mg/kg dose of aspirin to a cow might be quite toxic, the rumen (first stomach) acts in this case as an "anatomical sustained-release device," slowly releasing the aspirin into the intestine for subsequent absorption (flip-flop kinetics). This slow release helps avoid aspirin-induced toxicity but allows for the maintenance of therapeutic drug concentrations.

The microbial flora of the rumen is also problematic as many drugs are either partially or completely destroyed by this microenvironment. Conversely, severe gastroenteritis may result if the oral drug is an antimicrobial with a significant anaerobic spectrum. Still other disposition differences remain unexplained, such as why horses, although monogastrics, do not appreciably absorb any oral beta-lactams.

Pharmacodynamics can also vary by species. Aspirin inhibits platelet aggregation in humans, dogs, cats, and horses (perhaps its only practical use in the latter species), but not in cattle. Seemingly, thromboxane does not play a major role in the aggregation of bovine platelets. Opioids are another drug family in which receptor differences appear to account for species differences. Although morphine may be used in cats, it must be dosed at one half to one fourth the dose used in dogs and typically must be combined with a tranquilizer to avoid central nervous system (CNS) excitement. Conversely, intravenous doses of morphine toxic to dogs produce no change in the mentation of goats or cattle.

Beyond species differences, breed differences also are recognized. While most dogs easily tolerate 400 µg/kg of

Correspondence to:

Cory Langston

Telephone: (662) 325-3432

Facsimile: (662) 325-4011

E-mail: langston@cvm.msstate.edu

oral ivermectin daily (an extra-label treatment of demodectosis [red mange]), some collies develop CNS toxicity when receiving as little as a single oral dose of 100 µg/kg. This difference is apparently due to ivermectin accumulation within the CNS due to a deficiency of the P-glycoprotein pump in the blood-brain barrier of this canine breed. Genetic differences in metabolism, long noted in humans, are only now being investigated in animals.

While veterinary patients benefit from individual dose optimization of select drugs as do humans, species and breed differences are confounding variables that must be accounted for by the veterinary clinical pharmacologist. This is true whether the pharmacologist is involved in drug development, patient care, or teaching. Also, the approach one takes in delivering a therapy to an animal patient must be tempered by paradigms that differ from that in human medicine. For example, most owners of companion animals value the quality of life of their pet much more than they do the quantity of life. Also, decisions are often based on economic rather than emotional issues, particularly for the food animal client in which the patient is considered to be the herd or flock rather than an individual animal. In these situations, decisions on the practicality of medicating individuals versus the entire herd are extremely important from both logistic and economic perspectives. Last, public health concerns must be addressed. These include the avoidance of antimicrobial resistance (prudent antibiotic use); the avoidance of drug residues in milk, eggs, and meat from treated food animals; and environmental safety (eg, the environmental effects of active drug moiety in animal excreta or the impact of a drug added directly to an aquatic environment).

AMERICAN COLLEGE OF VETERINARY CLINICAL PHARMACOLOGY: HISTORY AND STATUS

Acknowledging the need to bridge the gap between pharmacology and veterinary clinical medicine, the American College of Veterinary Clinical Pharmacology (ACVCP) was established in 1990 and was recognized as a specialty by the American Veterinary Medical Association. By 1991, 11 additional diplomates entered the college through the successful completion of a 3-part examination (qualifying, certifying, and oral) administered by the 5 charter diplomates: Lloyd Davis, Tom Powers, Art Aronson, William Jenkins, and Charles Short. Since that time, the ACVCP has grown slowly but steadily. The process for determining individuals qualified to sit for examination evolved from submitting the credentials that establish their qualifications, to requiring

residency training (but allowing for nonconforming programs), to requiring training through an approved ACVCP residency. At present, a diplomate must meet the following requirements:

- Be legally qualified to practice veterinary medicine in a state, province, territory, or possession of the United States, Canada, or other country.
- Satisfactorily complete training under the supervision of a diplomate of the ACVCP. The training program must include all of the following:
 1. Advanced coursework, including a thorough understanding of pharmacodynamics, comparative pharmacology, analytical methods, pharmacokinetics, clinical therapeutic trial design, biostatistics, and pathophysiological processes and mechanisms of disease.
 2. Clinical experience, including 1 year of primary patient care or 2 years of clinical consultation.
 3. Research that addresses problems or that test hypotheses pertinent to veterinary clinical pharmacology.
- Publish 2 peer-reviewed scientific reports based on veterinary clinical pharmacology (review articles not allowed).
- Satisfactorily complete a qualifying examination.
- Satisfactorily complete a certifying examination. This exam is divided into essay sections that cover areas defined as "therapeutics" (4 questions), "pharmacokinetics and therapeutic drug monitoring" (2 questions), "experimental design, statistics, and analytical methodology" (2 questions), and "regulatory pharmacology" (2 questions). All questions contain multiple subsections. Therefore, the examination is given over an 8-hour period.

There are now 36 diplomates in the ACVCP. Their primary employment, as determined in a December 2001 survey, is depicted in **Figure 1**. The range of career paths of the diplomates gives insight into the roles that veterinary clinical pharmacologists have in animal health.

ACVCP Diplomate Employment, Dec 2001

Figure 1. Career paths of ACVCP diplomates. Academic basic indicates university assignment in a basic sciences department (eg, department of physiology and pharmacology); academic clinical, university assignment in a clinical department (eg, teaching hospital); industry management, pharmaceutical industry management; industry research, pharmaceutical industry with active research involvement; industry tech services, pharmaceutical industry providing professional (technical) services; regulatory, governmental regulatory agency; and inactive, diplomates no longer actively involved in pharmacology (eg, retired charter diplomates).

Figure 2. Subjective evaluation of the frequency with which various job responsibilities are encountered during the career of industrial veterinary clinical pharmacologists.

ROLES OF VETERINARY CLINICAL PHARMACOLOGISTS

What defines a veterinary clinical pharmacologist? The answer to this question remains a point of debate within the ACVCP. Notwithstanding a potential role for these individuals within regulatory pharmacology (as attested to by the employment of 2 diplomates within the Australian government), 3 primary schools of thought exist on this subject.

THE INDUSTRIAL VETERINARY CLINICAL PHARMACOLOGIST

Approximately 36% of the ACVCP diplomates have industry as their employment of choice. In this regard, one should note that 40% of the certifying exam covers experimental design, statistics, analytical methodology, and regulatory issues. This range of subjects reflects the belief that a veterinary clinical pharmacologist must be a competent scientist who can participate in or guide

Job duties of academic diplomates

Figure 3. Subjective evaluation of the frequency with which various job responsibilities are encountered during the career of academic diplomates.

clinical research efforts. The December 2001 survey results for the frequency distribution of job assignments of industrial veterinary clinical pharmacologists are provided in **Figure 2**. Whether in a research or a managerial role, a thorough understanding of drug product regulation is critical for the industrial clinical pharmacologist because a large portion of the duties may include "parenting" a new animal drug application through the various stages of an approval process. The ACVCP accreditation procedure ensures that diplomates have advanced training in these areas. This training enables the diplomate embarking on this career path to experience a much shorter "learning curve" than nondiplomate counterparts. Another argument for a strong industrial presence in veterinary clinical pharmacology is that this avenue provides the largest resource for monetary support of training programs as well as a more open avenue for employment of new diplomates.

THE ACADEMIC VETERINARY CLINICAL PHARMACOLOGIST - BASIC SCIENCE APPOINTMENT

Defining the role of the veterinary clinical pharmacologist in academia has been difficult. Traditionally, pharmacology positions have been associated with the basic science departments. This is reflected in that 30% of diplomates have their primary duties within such departments. As noted in **Figure 3**, large portions of their full-time equivalent are devoted to the traditional science endeavors of clinical research and teaching. As non-veterinarian physiologists and pharmacists increasingly are teaching veterinary school pharmacology courses, the opportunity for an ACVCP diplomate to relate basic science concepts to actual patient care is becoming particularly important to veterinary students. This input also represents an important mechanism through which diplomates may ensure rational drug use by future practitioners. In this regard, many such academicians also offer clinical pharmacology electives, usually for

senior veterinary students, to further reinforce these important concepts. Diplomates have the opportunity to further influence patient care by providing expert consultation to clinicians and by offering (and interpreting) therapeutic drug monitoring.

Of great concern to veterinary clinical pharmacologists within a basic science department is whether or not they will be supported and rewarded for their endeavors. Increasingly, such departments have focused their interests on tenure-track faculty who obtain competitive research (basic/molecular biology) grants. Little if any value often is placed on clinical service and teaching (as judged by the achievement of tenure). Therefore, whether or not the veterinary clinical pharmacologist will flourish within an academic basic science setting will most likely depend on the perceived importance of the discipline by his or her department head. If the administration supports and rewards applied research, clinical service, and teaching, the diplomate can prosper. Conversely, if the administration is centered on grantsmanship and basic research productivity, the diplomate risks either nontenure or forced diversion from a "clinical" focus.

THE ACADEMIC VETERINARY CLINICAL PHARMACOLOGIST - CLINICAL APPOINTMENT

At its inception, consideration was given to establishing the specialty of veterinary clinical pharmacology as a subspecialty of the American College of Veterinary Internal Medicine (ACVIM). Such distinctions within ACVIM already exist for the areas of cardiology, neurology, and oncology. While the decision was ultimately to forgo this approach in favor of a separate college, 20% of diplomates have elected to have primary clinical appointments. In all instances, these diplomates have primary patient care or herd health duties. With these duties, these diplomates arguably are optimally positioned

not only to ensure rational drug therapy for their own patients but also to influence the therapeutic decisions of their fellow clinicians, and perhaps more importantly, the veterinary student. Students tend to use the same therapies that they see applied in teaching hospitals and in their preceptorships. Therefore, while a recommendation for therapy may be made in the classroom, the student is likely to ignore it if he or she does not see it applied in the clinical setting.

Does this imply that those without direct patient care responsibilities do not impact rational drug use? Obviously, this is not the case; however, the nonclinician's ability to influence patient care and drug use probably depends on how often he or she is called upon by those in the clinics, which depends on his or her credibility. ACVCP clinicians establish this credibility on a regular basis through their own patient care while nonclinicians must develop it over a longer time frame through their availability for consultation and the utility of their recommendations.

As the academic nonclinician faces obstacles by working in a basic science department, so does the academic clinician face obstacles by working in a clinical department. Most clinical departments are teaching hospitals where the primary emphasis is on patient care, the training of veterinary students, and the generation of income. It is difficult to argue that a teaching hospital should hire a clinical pharmacologist if that individual is not addressing all of these needs, when that same money could be spent instead on a surgeon or internist who might better accomplish each of these responsibilities. Therefore, it is no surprise that most diplomates with clinical appointments are hired because of an expertise in a specialty other than pharmacology. Just as the nonclinician must have administrative support to pursue a clinical rather than a basic science role within a department, to prosper in a clinical setting, the ACVCP clinician must have support to pursue pharmacology interests (eg, applied research) in addition to his or her clinical service duties.

ISSUES FOR THE FUTURE OF VETERINARY CLINICAL PHARMACOLOGY

The distinctiveness of clinical pharmacology may best be explained by contrasting it with the 2 fields with which it shares many common interests: basic pharmacology and internal medicine. By focusing on the application of basic pharmacology within the clinical milieu, the field of clinical pharmacology provides a vital bridge between rational drug selection, clinical pharmacokinetics, therapeutic drug monitoring, drug interactions, and drug-induced adverse effects. While such expertise is vital to the practice of internal medicine, it relies on a foundational understanding of basic pharmacology that goes well beyond the traditional domain of internal medicine. In addition, clinical pharmacology addresses issues pertinent to drug development, drug approval, and the regulation of drug use. These activities involve biomedical research and are critical to clinical medicine by allowing for the availability of the therapeutic arsenal needed to

support current clinical veterinary practices and to provide the regulatory framework essential to ensuring successful drug therapy.

The role of the veterinary clinical pharmacologist in industry and in the academic basic sciences seems well established and justifiable. Unfortunately, the position of the diplomate as an academic clinician is far more tenuous. If that role is to prosper, the development of residency programs that prepare candidates for dual certification within ACVIM and ACVCP would be desirable. To ease the burden of this task, perhaps subspecialties within the ACVCP would be appropriate. For example, for the more clinically inclined, less emphasis might be given to experimental design, statistics, analytical methodology, and regulatory issues. Residency programs could be created to prepare candidates for dual certification within ACVIM and ACVCP. Likewise, specialization in research and regulatory pharmacology might be a track to develop.

Are there enough individuals within each subspecialty to warrant the development of alternative tracks or has the current trend away from clinical patient care already decided the issue? Would subspecialization benefit or balkanize the ACVCP? Both are questions for further consideration. Nevertheless, the evidence is clear: the veterinary clinical pharmacologist has a pivotal role in maintaining the optimization of therapeutic practices for both food and companion animal medicine. Therefore, it is our responsibility to ensure that this specialty continues to thrive for the future generations of our veterinary health profession.

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