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Fiona Cunningham • Jonathan Elliott • Peter Lees
Editors

Comparative and Veterinary Pharmacology

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Editors

Fiona Cunningham
Royal Veterinary College
Dept. Veterinary Basic
Sciences
Hawkshead Lane
Hertfordshire
United Kingdom AL9 7TA
fcunning@rvc.ac.uk

Jonathan Elliott
Royal Veterinary College
Dept. Veterinary Basic Sciences
Royal College Street
London NW1 OTU, UK
jelliott@rvc.ac.uk

Peter Lees
Royal Veterinary College
Dept. Veterinary Basic
Sciences
Hawkshead Lane
Hertfordshire
United Kingdom AL9 7TA
plees@rvc.ac.uk

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Preface

The human–animal bond has evolved and diversified down the ages. Dogs, cats and even horses, have long fulfilled the role of faithful companion and indeed, as exemplified by the introduction of seeing and hearing dogs, there may be a critical level of co-dependency between the species. In the twenty-first century, the animal types that are kept as pets in many parts of the world are extensive ranging from reptiles through rodents to ruminants and beyond. As would be predicted by the nature of the relationship, the approach to treatment of a companion animal is often closely aligned to that which would have been offered to their owner. However, an increasing awareness of welfare issues, such as the recognition that animals experience pain and the proven benefits of disease prevention in intensive farming units, together with the growth in zoos and wildlife parks, has increased the likelihood of food producing and non-domesticated animals receiving medicinal products during their life-time.

Although many of the individual drugs or classes of drugs administered to animals are the same as, or derived from, those given to man, the safe and effective use of drugs in animals often cannot be achieved by simply transposing knowledge of drug action on, or behaviour in, the body from one species to another. The impact of the anatomical, physiological and pathophysiological variability that spans the animal kingdom can often profoundly alter drug response. Thus the discipline of veterinary pharmacology, which has grown up alongside and developed from basic and medical pharmacology, has drawn from and built upon, but has sometimes had to markedly adapt data obtained from drug use for the prevention and treatment of disease in man. In compiling this volume, Springer Verlag has provided us with the opportunity to collaborate with world experts in this field in order to bring together a series of succinct overviews in some key areas of veterinary pharmacology and therapeutics. Those topics addressed in the first part of the volume (Chaps. 1–7) illustrate both the commonality and differences between drug pharmacodynamics and pharmacokinetics in animals and man, looking also to the future benefits that introduction of new technologies may bring. Those in the latter part (Chaps. 8–12) demonstrate the potential impact of drug use in animals on man and the

environment, as well as presenting the many benefits to man brought about by the genetic modification of animals.

We hope that you will enjoy reading this volume as much as we, the editors, have enjoyed our role in its creation.

October 2009

Fiona Cunningham
Jonathan Elliott
Peter Lees

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Contributors

Alan W. Baird School of Agriculture, Food Science and Veterinary Medicine, University College Dublin and UCD Conway Institute, Belfield, Dublin 4, Ireland, alan.baird@ucd.ie

Hafid Benchaoui Novartis Animal Health, Research & Development, Schwarzwaldallee 215, WRO-1032.2.44, CH-4002, Basel, Switzerland, hafid.benchaoui@novartis.com

Alain Bousquet-Mélou Unité Mixte de Recherche 181 Physiopathologie et Toxicologie Expérimentales, Institut National de la Recherche Agronomique et, Ecole Nationale Vétérinaire de Toulouse, 23 Chemin des Capelles, BP 87 614, F-31076 Toulouse cedex 3, France, a.bousquet-melou@envt.fr

Alistair B.A. Boxall Environment Department, University of York, Heslington, York, YO10 5DD, UK, abab500@york.ac.uk

David J. Brayden School of Agriculture, Food Science and Veterinary Medicine, University College Dublin and UCD Conway Institute, Belfield, Dublin 4, Ireland, david.brayden@ucd.ie

Michael H. Court Department of Pharmacology and Experimental Therapeutics, Tufts University, School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA, michael.court@tufts.edu

Fiona Cunningham Department of Veterinary Basic Sciences, Royal Veterinary College, Hawkshead Lane, North Mymms, Hertfordshire AL9 7TA, UK, fcunning@rvc.ac.uk

Jonathan Elliott Department of Veterinary Basic Sciences, Royal Veterinary College, Royal College Street, London NW1 OTU, UK, jelliott@rvc.ac.uk

Aude Ferran Unité Mixte de Recherche 181 Physiopathologie et Toxicologie Expérimentales, Institut National de la Recherche Agronomique et Ecole Nationale Vétérinaire de Toulouse, 23 Chemin des Capelles, BP 87 614, 31076 Toulouse cedex 03, France, a.ferran@envt.fr

Robert P. Hunter Elanco Animal Health, 2001 West Main Street, Drop Code GL 36, Greenfield, IN 46140, USA, hunterrp@lilly.com

Peter Lees Department of Veterinary Basic Sciences, Royal Veterinary College, Hawkshead Lane, North Mymms, Hertfordshire AL9 7TA, UK, plees@rvc.ac.uk

Alex Livingston Department of Veterinary Biomedical Sciences, Veterinary Medicine Building, University of Saskatchewan, 52 Campus Drive, Saskatoon, Saskatchewan, Canada, S7N 5B4, alex.livingston@usask.ca

Marilyn Martinez Office of New Animal Drug Evaluation (HFV-130), Center for Veterinary Medicine Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, USA, marilyn.martinez@fda.hhs.gov

Carrie M. Mosher Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA

Emilie M. Oudot School of Agriculture, Food Science and Veterinary Medicine, University College, Dublin and UCD Conway Institute, Belfield, Dublin 4, Ireland, emilie.oudot@ucd.ie

Philip T. Reeves Australian Pesticides and Veterinary Medicines Authority, PO Box 6182, Kingston ACT 2604, Australia, Phil.Reeves@apvma.gov.au

Jim E. Riviere Center for Chemical Toxicology Research and Pharmacokinetics, Department of Population Health and Pathobiology, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606, USA, jim_riviere@ncsu.edu

Peter Silley Consult Limited, Enterprise House, Ocean Village, Southampton, Hampshire, SO14 3XB, UK, p-s@mbconsult.co.uk

Pierre-Louis Toutain Unité Mixte de Recherche 181 Physiopathologie et Toxicologie Expérimentales, Institut National de la Recherche Agronomique et Ecole Nationale Vétérinaire de Toulouse, 23 Chemin des Capelles, BP 87 614, 31076 Toulouse cedex 03, France, pl.toutain@envt.fr

Dominic J. Wells Department of Veterinary Basic Sciences, Royal Veterinary College, London NW1 OTU, dwells@rvc.ac.uk

Part I
Topics in Veterinary Pharmacology

Introduction

Fiona Cunningham, Jonathan Elliott, and Peter Lees

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1 From Materia Medica to Veterinary Pharmacology and Therapeutics

The origins of veterinary pharmacology and therapeutics are the same as those of the equivalent human disciplines, lying in the administration of and responses to plants and extracts of plants containing pharmacologically active compounds. The history of Materia Medica, and then the emergence of pharmacology and therapeutics in humans have been extensively described. Appelgren (2009) has provided a recent summary of both the human and parallel veterinary developments. He describes the early records contained: (a) in Egyptian papyri (1800–1200 BC), the contents of which became known only from 1822 when the Rosetta stone was translated and; (b) in the writings of the Greeks (notably Hippocrates, 430 BC) and later Galen (94 AD). Hippocrates' and Galen's prescriptions dominated European medicine for many centuries, through the medieval periods, until superseded in the Age of Enlightenment. As Appelgren points out, we can certainly conclude that

F. Cunningham and P. Lees (✉)

Department of Veterinary Basic Sciences, Royal Veterinary College, Hawkshead Lane, North Mymms, Hertfordshire AL9 7TA, UK

e-mail: fcunning@rvc.ac.uk; p Lees@rvc.ac.uk

J. Elliott

Department of Veterinary Basic Sciences, Royal Veterinary College, Royal College Street, London NW1 0TU, UK

e-mail: jelliott@rvc.ac.uk

the same “drugs” were used in animals and man up to and beyond the Age of Enlightenment. There was, however, at this time an expression of concern relating to the use of drugs therapeutically in animals on the basis of human experience. As voiced by the Swedish botanist and doctor Carolus Linneaus, “human medicines are used for animals without knowledge if they work, which is devastating barbarism”. At that time much of the progress in veterinary medicine was made in France, and Linneaus sent Peter Hernquist to France to learn the scientific principles underlying veterinary medicine. In 1791, Charles Vial de St. Bel left the Lyon school to found the first veterinary teaching establishment in the English speaking world, the Royal Veterinary College in London, later to become a constituent College of the University of London.

A key development in the emergence of the science of pharmacology, from the older discipline of *Materia Medica*, was the progress in organic analytical and synthetic chemistry in the early to mid nineteenth century. One example will suffice to illustrate this historical development, through to the twenty-first century. The therapeutic properties of the leaves and bark of the willow tree had been described in the first century AD by Dioscorides in his pharmacopoeia. Several centuries prior to the birth of Christ, Aristotle had similarly used extracts of the willow to ease the pain of childbirth in humans. The benefits of the willow might have remained as a small historical footnote had the Reverend Edward Stone of Chipping Norton, UK not revived interest in his *Philosophical Transactions* to the Royal Society.

In the first half of the nineteenth century, chemists isolated from the willow a glycoside, saligenin, one component of which was shown in 1830 to be salicyl alcohol. Recognising this as the active principle of saligenin, chemists converted this to salicylic acid and then to its sodium salt. Finlay Dun (1895) described the therapeutic value of sodium salicylate in the horse and dog, for its analgesic action in joint diseases. We now know that the pathology of degenerative joint disease in these species shares many common features with that occurring in the ageing human population and that the natural wear and tear process is accelerated by extreme activity or sub-optimal conformation.

In 1898, Felix Hoffmann of the Bayer Pharmaceutical Company described the use of the acetyl ester of salicylic acid (aspirin) in his arthritic father and the next phases through to the twenty-first century led to the introduction of successive agents of the non-steroidal anti-inflammatory drug (NSAID) class. However, it was not until 1971 that Vane (1971) discovered the principal mechanism of action of NSAIDs to be inhibition of cyclo-oxygenase (COX), an enzyme which converts the substrate arachidonic acid to a range of locally acting autacoids, described under the collective term eicosanoids. Eicosanoids possess a wide range of properties that include the generation *de novo* of compounds such as prostaglandins (PG) E_2 and I_2 , which exert crucial roles as mediators of acute inflammation, notably in the phenomenon of hyperalgesia, through both local and central actions. It was not until 1991 that the discovery of two COX isoforms, COX-1 and COX-2, led to the concept that the former was involved primarily in a range of protective roles, while the latter was involved mainly in generating inflammatory mediators.

In terms of pharmacodynamics, the veterinary history of NSAIDs has followed human developments, so that the latest phases have included the introduction into veterinary therapeutics of the dual inhibitor class of COX and 5-lipoxygenase (e.g. tepoxalin) and the preferential/selective class of inhibitors of the COX-2 isoform, the COXibs. Veterinary medicine now has five drugs of this class, either in use or currently under review by regulatory bodies, cimicoxib, deracoxib, firocoxib, mavacoxib, and robenacoxib. While the study of the pharmacodynamic properties of novel NSAIDs has followed, in qualitative terms, the developments in human pharmacology and therapeutics, it may be noted that quantitatively significant differences exist between humans and other animals, and between animal species. Thus, there are species differences in potencies for inhibition of the COX-1 and COX-2 isoforms and in COX-1:COX-2 potency ratios. An example is carprofen, which has been shown to be COX-2 preferential in the dog and cat, COX non-selective in the horse, and COX-1 selective in man (Warner et al. 1999; Lees et al. 2004).

It may also be noted that species differences in some pharmacokinetic properties of NSAIDs have been found, in general, to be minor, but for other properties the differences have been marked. Thus, most NSAIDs are highly protein bound and have small distribution volumes (V_{darea} and V_{dss}). On the other hand, differences between species in clearance and elimination half-life are the rule rather than the exception. This is exemplified by phenylbutazone for which elimination half-life values in hours have been determined: 96 (man), 60 (cow), 18 (sheep), 16 (goat), 13 (camel), 5 (horse and dog), 3 (rat), and 2 (donkey) (Lees et al. 2004). Likewise, the pharmacokinetics of aspirin, vary markedly between species. In all species, the drug is rapidly deacetylated to salicylate (the half-life of aspirin in the horse, for example, is 9 min) and the elimination half-life of salicylate in hours varies significantly between species: 22–45 (cat), 8.6 (dog), 5.9 (pig), 3.0 (man), 1.0 (horse), and 0.5 (cow) (Lees 2009). The cat illustrates another aspect of species variability in pharmacokinetics, in that elimination of salicylate is zero order, so that the half-life increases with dose, in consequence of saturation of the elimination pathways.

The pharmacodynamic consequences of COX-2 inhibition are beginning to emerge, with adverse events being reported from the large clinical trials conducted using COXibs. The increased prevalence of acute cardiovascular events in human patients on chronic COXib treatment was unexpected and may be explained by the physiological importance of COX-2 in the endothelium. As the use of COXibs becomes more widespread in dogs, cats and horses, it seems likely that pharmacodynamic species differences, possibly affecting the gastrointestinal and renal systems, will emerge in veterinary pharmacology.

The science of pharmacogenomics is now firmly established as a sub-branch of pharmacology, with many reported differences in the pharmacokinetic properties of various drug classes between differing human racial groups. In veterinary medicine, pharmacogenomics is much less well established but, if clear differences commonly exist between racial groups in humans, differences can likewise be expected between differing breeds of, for example, dogs. The literature evidence is very limited, but clear differences have been shown to occur between mongrel dogs and

beagle dogs for the anti-epileptic drugs phenobarbitone and the NSAID naproxen, the beagle breed having the shorter elimination half-life.

In addition to the well established pharmacokinetic inter-species differences and the, although still largely un-researched, likelihood of inter-breed differences, there is the equal likelihood of intra-breed differences. Again, there are very limited available data, but the study of Paulson et al. (1999) on the COX-2 inhibitor celecoxib clearly showed that dogs of the Beagle breed could be classified into PM or EM groups, “poor” and “extensive” metabolisers, respectively. With the dog genome having now been sequenced and the high degree of relatedness that is recognised within individuals of a given breed because of genetic bottlenecks, it is likely that, in the future, the dog may be an excellent model to determine the genetic basis for particular pharmacological phenotypes that are shared between human and veterinary medicine.

The next phase in gaining increased knowledge of the pharmacology of NSAIDs in species of veterinary interest (as yet still very incomplete) is the recognition that animals in a clinical population, comprising usually many differing breeds and including also animals of varying weight and in various states of health, will almost always have a greater range of values of pharmacokinetic parameters, such as clearance and elimination half-life, which (in part) determine effective dosage schedules. In addition, in clinical populations, the means (as well as range) of values may vary from those determined in healthy animals in pre-clinical studies. This has been shown for two drugs of the COXib class, mavacoxib and robenacoxib, in dogs clinically affected with the condition of osteoarthritis. In both cases, clearance was slower and terminal half-life longer than the values obtained in pre-clinical studies in healthy animals (Cox et al. 2009; Giraudel et al. 2009; Lees 2009).

In veterinary medicine, the transition from *materia medica* to veterinary pharmacology occurred slowly from the early to mid twentieth century. The discoveries and introduction into veterinary therapeutics of sulphonamides, benzylpenicillin, and then the streptomycins as antimicrobial drugs, of NSAIDs such as phenylbutazone, of sedatives such as acepromazine, of volatile anaesthetics such as halothane, and of injectable anaesthetics of the barbiturate class laid the early foundations of veterinary pharmacology and therapeutics in the period 1930–1960. Nevertheless, at the time of appointment of one of the editors (PL) to the staff of the Royal Veterinary College in 1964, there remained in widespread use older drugs. These included phenothiazine (as an anthelmintic), carbon tetrachloride (as a treatment for liver fluke infestation), chloral hydrate (as a sedative), chloroform (as an anaesthetic), a range of digitalis glycosides (for the control of congestive heart failure), and organomercurials (as diuretics), all of questionable efficacy and/or low safety in clinical use.

Within the 50 year period from 1960 to 2010, veterinary pharmacology and therapeutics have been transformed. This has occurred first through major advances in understanding disease (both infectious and non-infectious) mechanisms at molecular, cellular, organ and whole animal levels and secondly (and in consequence) through the introduction of drugs with increasingly selective actions. In parallel, the identification of drug action at receptor and enzyme levels has led to

improved targeting of therapeutic agents. The veterinary pharmacologist has taken advantage of new knowledge in basic science that leads to drug discovery. Often drugs have been developed for human clinical use before they have been investigated in veterinary clinical patients. Safety and efficacy cannot be assumed to apply across species (e.g. α_2 -adrenoceptor agonist drugs lack sedative efficacy in pigs; ibuprofen has a very narrow therapeutic index in dogs) and careful study in each individual species is required. Likewise, some drugs discarded at an early stage of development for human medicine, prove to be highly efficacious and safe in some veterinary clinical patients (e.g. milrinone in treating dilated cardiomyopathy in dogs). The beneficial result has been the introduction of many novel drugs with increased efficacy and reduced toxicity for human and veterinary use. Some 95% plus of drugs now in widespread clinical use were undiscovered in 1960.

2 Aims of This Volume and Rationale for Inclusion of the Chapters

As the short introduction above illustrates, the discipline of veterinary pharmacology has evolved alongside that of human pharmacology. While the two may, on the face of it, be regarded as essentially similar, there is no doubt that species and breed differences in pharmacokinetics and pharmacodynamics can have a significant impact on the approach to, and outcome of, drug use in animals. It is also the case that between species comparative studies can of themselves inform knowledge of the properties and actions of drugs that are to be used in animals and man. Thus, the principal aims of this volume are twofold. The first aim is to illustrate those aspects of veterinary pharmacology that are unique and the second is to demonstrate the alignment between, as well as the impact on human health of, the use of drugs in animal and human populations.

In the first chapter of this text, Toutain and colleagues review a very large subject, namely the differences between species in pharmacokinetic and pharmacodynamic properties of drugs. Differences between species in drug action have been defined, for example, for COX-1 and COX-2 inhibitors (*vide supra*), but the literature is not extensive in this area and in the absence of data it is commonly assumed (no doubt often incorrectly) that they do not exist or are insignificant.

From the very extensive literature on inter-species variability in drug pharmacokinetics, on the other hand, it is clear that there are both qualitative (inability of dogs to acetylate, cats to glucuronidate drugs, etc.) and quantitative (markedly differing and commonly unpredictable differences in pharmacokinetic parameters, notably clearance and half-life) differences between species. The required dose of any systemically acting drug, for a given pharmacological or therapeutic response, is determined by two pharmacokinetic properties, clearance (Cl) and bioavailability (F) and one pharmacodynamic parameter, potency (usually expressed as 50% of maximum attainable response, EC_{50}):

$$ED_{50} = \frac{CI \times EC_{50}}{F},$$

where ED_{50} is the dose providing 50% of the maximum response.

As the veterinary clinician has to deal with seven major (horse, dog, cat, pig, cow, chicken and sheep) and many more minor species (including several fish species), it is clear, from the likely inter-species variability in pharmacokinetics and the possible differences in pharmacodynamics, that doses must be set on an individual species basis. Similar considerations apply within a given species, in relation to possible inter- and intra-breed differences. Also reviewed in this chapter are factors such as individual animal versus group/herd treatment, the former being the norm for companion animal species, such as horse, dog, and cat, and the latter being common in farm animal, fowl, and fish therapeutics. This subject is further reviewed in the contribution by Benchaoui. The origins of inter-species, inter-breed, and inter-animal differences are explored in detail. An interesting example, very clearly distinguishing some animal species from humans is coprophagia, a practice which can lead to “a second dose” of drugs. Special considerations apply also to drug action and disposition in poultry and fish species, in consequence of anatomical and physiological differences from mammals, as well as species specific disease conditions. It is predictable that future advances in pharmacogenetics and pharmacogenomics, together with the results of population pharmacokinetic and pharmacodynamic studies, will lead to increased knowledge of mechanisms causing inter-species differences and thereby facilitate the design of more rational dosage regimens.

Mosher and Court extend the basic concepts outlined in the contribution of Toutain and colleagues. Comparative and veterinary studies of pharmacogenomics are providing a novel basis for explaining inter-species, inter-breed and even intra-breed differences in both pharmacokinetic and pharmacodynamic properties of drugs. While still at an early stage of development, animal pharmacogenomics has as its ultimate goal the design of dosage schedules that are optimal for sub-groups (breeds, young vs. old animals, etc.) or even provide individualised dosing regimens. Thus, P4502D15 and P4501AZ polymorphisms in beagle dogs explain the identification of sub-groups classified as poor (PM) or extensive (EM) metabolisers. The well-defined slower metabolism of thiobarbiturates in Greyhounds compared to mixed-breed dogs is consistent with a lack, in Greyhounds (and related breeds), of one or more P450 isoforms. It is likely that this is due to lower expression of CYP2B11.

Important pharmacogenomic variations have also been described for the transporter enzymes, *P*-glycoprotein (*P*-gp) in dogs and mice. The importance of *P*-gp was discovered when knock-out mice lacking MDR-1 gene were treated for a parasitic infestation with ivermectin. These mice died showing neurological signs, whereas the wild type controls showed no adverse signs. A veterinary pharmacologist read the report of this study and wondered whether a polymorphism in the gene explained the sensitivity of Collie types of dog to therapeutic doses of ivermectin used to treat mange mites in the dog (Mealey et al. 2002). This proved to be the case. Pharmacogenomic variation in dogs of *P*-gp, an efflux transporter

located in intestine, liver, kidney, and brain, involving loss of function, leads to increased brain penetration of certain drugs of which ivermectin is the most studied.

Brayden and colleagues review the many aspects of drug delivery either from sites of administration to the circulation or from the circulation to sites of action. A wide range of species specific devices and product formulation approaches to drug delivery are now used in veterinary medicine. These are designed to deliver therapeutic agents at either constant or variable rates for pre-determined times to suit a wide range of species and disease conditions and to meet the needs of both individual animals and herds. This chapter compares and contrasts the technologies and formulations used in animals with those used in humans. The greatest differences are between farm animal and fish species and humans. Thus, in farm animal medicine, where repeated administration of drugs to grazing animals throughout the season is impractical, much use is made of slow release technologies. A single administration can provide relatively constant drug levels over weeks or longer and is equivalent to constant intravenous infusion. Other devices have been designed to provide pulsatile release of anthelmintics such as oxfendazole, the time between the pulses corresponding to just less than the pre-patent period of the nematodes ensuring ingested eggs develop into susceptible stages but are eliminated before they produce eggs which further contaminate the pasture.

In veterinary therapeutics, there are many examples of topical formulations designed to deliver drugs, e.g. insecticides locally for external parasite infection control as well as for systemic absorption through the application of skin patches (e.g. the opioid analgesic fentanyl) or the use of “pour on” products which deliver drugs, e.g. anthelmintics transdermally. An interesting complication of this route is the self-licking and licking of companions leading inadvertently to drug delivery orally as well as transdermally, with the unintended consequence of increased inter-animal variability in dosage received.

Brayden and colleagues also address the rapidly increasing interest in the role of endogenous drug transporters in regulating drug delivery. Expression of ABC transporters confers multi-drug resistance in tumour cells and the resistance of bacteria to antimicrobial agents. Other roles, for example, as efflux transporters in enterocytes and blood–brain barrier endothelial cells, are being actively researched, as is their potential as a cause for drug interactions.

Benchaoui reviews the economic and welfare requirements for, and means of, implementing population medicine in the veterinary care of both livestock and companion animals. The aim of population medicine is the control, and ideally eradication, of infectious and parasitic diseases, in order to ensure the welfare, health, and productivity of livestock through the implementation of whole herd strategies. While control is commonly achieved through the use of vaccines, there remains a major role for the use of chemotherapeutic agents, particularly anthelmintics and antimicrobial drugs, for the treatment of worm and bacterial diseases, respectively.

Population medicine is now a huge discipline and this chapter therefore focuses on selected examples. A major area of concern is the gastrointestinal and liver parasitisms of grazing cattle and sheep, requiring strategically timed anthelmintic medication, a subject also considered in the immediately preceding chapter. An

interesting aspect of increasing importance is the growth of organic farming, wherein the use of anthelmintic drugs is generally restricted. Some cases of poor management on organic farms have resulted in avoidable clinical parasitism in sheep. Other parasitisms in dogs and cats require differing therapeutic approaches.

The two other examples discussed in this chapter relate to bacterial diseases, one of adult cattle and one of calves and young pigs. The pathogens causing intramammary infections in adult dairy cattle are many, but they are primarily bacteria, thus requiring antimicrobial drug treatment while animals are lactating and prophylaxis for prevention at “drying off”. In both circumstances, drugs or drug combinations providing a broad spectrum of activity are required, but in the lactating animals products with a short duration of action are infused into the udder, commonly twice daily for 1–3 days, while in the “dry period” the formulations are designed to maintain antimicrobial levels over several weeks.

The second example of bacterial infection leading to major welfare and production loss issues are the pneumonic conditions which affect calves and piglets. Causative pathogens include viruses and bacterial species, including *M. haemolytica*, *P. multocida*, and mycoplasma species. Infections are commonly mixed. As there are no effective antiviral drugs, therapy is directed against the bacterial and mycoplasma species which either induce disease or are secondary opportunistic pathogens. Drugs of several classes are used and much research has been directed to optimising pharmacokinetic properties through the use of drugs which accumulate in lungs in high concentrations. Several antimicrobial drug classes possess anti-inflammatory and/or immunomodulating properties and there is debate on the extent to which the host effects of, for example, macrolide drugs contribute to therapeutic success.

A common concern arising from the use of both anthelmintic and antimicrobial drugs is the emergence of resistance. In the case of antimicrobial drugs, this concern relates not only to the loss of efficacy in treating animal diseases, but also the possibility of spread of resistance from animals to man, and indeed, from humans to animals also. This topic is also dealt with in greater detail in the chapter of Martinez and Silley.

Several chapters in this text review the impact on the pharmacokinetic and pharmacodynamic properties of drugs arising from species differences. These differences have been addressed through experimental studies in the major veterinary species. However, extending the studies to exotic, wildlife, and zoo species is, in many instances, impractical and economically not feasible. On the other hand, the approach of “trial and error” to selecting drugs and predicting pharmacokinetic and pharmacodynamic properties and hence dosage schedules for such species is scientifically unsound. Hunter reviews the anatomical and physiological differences between species, in relation to their likely impact on the pharmacokinetics and pharmacodynamics of drugs and describes the approaches that have been made to prediction of species variability. The simplest but almost invariably flawed approach is to base dose on body weight, irrespective of body size; this assumes a linear increase in dose with increasing body weight. Allometric scaling is a superior alternative, based on a log–log relationship, first applied in the 1930s to relate metabolic functions to body size.

The chapter by Hunter illustrates the “successes” and “failures” in extrapolating clearance data (a) between mammalian and avian species, (b) between avian species and (c) between various “large” animal species. Drugs which have been found generally to be good candidates for allometric scaling include carbenicillin, diazepam and prednisolone. However, this list is outnumbered by drugs such as paracetamol, fentanyl and xylazine which have been shown to be poor candidates.

Livingston reviews current thinking on mechanisms of pain and its relief in a wide range of animal species, including the human animal. While there are differences of detail, the neuronal pathways, transmitters and receptor types are broadly similar in all mammals and probably also in all vertebrates. However, a crucial difference between man and other animals is the ability of the adult human in most circumstances to describe through verbal communication their perception of pain, including its type, intensity and duration. Therefore, both the evaluation of pain and its relief through the actions of analgesic drugs is assessed in non-human animals differently, by behavioural responses. The problems in studying pain intensity and drug-based alleviation of pain relate not only to the absence of verbal communication, but also to the fact that differing pain stimuli often produce different responses within a species. Moreover, for a similar stimulus, the behaviours vary markedly between species.

In assessing pain, it is necessary to recognise that humans and their close relatives vocalise and display marked escape behaviour and enlist peer support with the objective of avoiding or ameliorating pain. Vocalisation is also characteristic of dogs, whereas animals living in large groups and possibly subject to the attention of predators may react in a less overt manner and this has been regarded as an important element in their survival strategies. In circumstances such as these, should an animal display overt signs of pain, its ability to escape would be reduced. Therefore, the behavioural responses used to assess pain and analgesia differ between the monkey and the sheep and so on.

Many of the pain behaviours used in experimental and clinical pain therefore involve subjective and species dependent assessments, made using semi-quantitative indices of severity (e.g. numerical rating scales) or continuous scales (e.g. visual analogue scales). However, there is increasing use of more objective indices, for example, for assessment of joint pain through the use of force plate analyses.

Riviere offers informed speculation on the manner and extent to which new technologies could transform veterinary therapeutics over the next 30 or so years. All futuristic predictions necessarily comprise a risk exercise, but Prof Riviere is well placed to undertake this task through his own background in technology transfer. Whether at all and to what extent the predictions are realised will depend on several interacting factors, which themselves contain unknowns and uncertainties, relating to societal demands and trends as well as economic issues. To what extent will global financial crises stifle development? Will the global warming consequences of emission of methane and the high conversion cost of generating calorific protein in the cow spell its total or partial demise? These considerations notwithstanding, this chapter reviews the nature of, and potential for, application to

veterinary pharmacology and therapeutics of six areas of endeavour, emphasising the potential for interaction between them:

- (a) Further advances in computer technology
- (b) Microfluidics
- (c) Nanotechnology
- (d) High-throughput screening
- (e) Increased control and targeting of drug delivery
- (f) Increased knowledge of pharmacogenomics

The last two of these fields are further discussed in the chapter by Brayden and colleagues and the developments in pharmacogenomics are also addressed in the contribution of Mosher and Court.

The first transforming factor, computer technology, will certainly play a prominent role in veterinary pharmacology and therapeutics through, for example, even more sophisticated programmes of population pharmacokinetics and pharmacokinetic–pharmacodynamic modelling of data, and similar parallel developments in veterinary toxicology can be anticipated. There will also be further advances in integrating genomic and proteomic data with physiologically based pharmacokinetic models. These models will lead towards development of dosing schedules on individual herd and sub-group bases, as also discussed by Toutain and colleagues.

Microfluidic devices have arisen through computer processor miniaturisation and advances in microscale engineering; these devices allow complete analytical platforms to be contained on the size of a postage stamp. The prospect is for linking these devices to implantable, feed-back controlled, drug delivery devices. Further, these devices may be powered by endogenous ionic substances to energise the internal batteries. The selection of antimicrobial drugs might be facilitated by devices which identify specific genetic determinants of resistance.

Nanotechnology utilises manufactured materials which are less than 100 nm across one dimension and possess unique physical properties. The potential is for the use of nanomaterials as drug carriers targeted to selected organs/tissues, reducing dose and increasing drug safety. The therapy of cancers is the area of greatest promise. Beyond that, they may be used to create artificial ribosomes and even wholly manufactured cells. The cautionary note is that the toxicology of nanomaterials remains to be fully defined.

Wells reviews the use of genetically modified animals in research and the benefits deriving from increasing knowledge of genomes in domestic animal species. Genetic manipulations have been (and will increasingly be) used to investigate specific gene functions, to provide models of human diseases, to treat inherited and spontaneous diseases, and to increase resistance to disease. This chapter traces the history of genetic modifications in pharmacological research, considers recent advances such as the development of induced pluripotent stem cells for increasing the efficiency of producing gene targeted domestic animals, and reviews future prospects. While genetically modified mice have been crucial in understanding gene function, especially in relation to human diseases, there have been (on a lesser scale) transgenic farm animal developments to provide resistance

from disease and to generate nutritionally enhanced food, as well as for facilitating xenografting.

A vast number of murine models of human disease have been developed, which have been invaluable for testing novel therapeutic agents. Knock-out mice have also played important roles in furthering understanding of a wide range of physiological and pathological mechanisms. Nevertheless, mouse models are not without limitations and large animal models, or naturally occurring diseases in veterinary clinical patients, may, in some circumstance, provide more appropriate alternatives.

From the perspective of future advances in veterinary therapeutics, the development of sequencing the genomes of several major veterinary species may be noted. For example, the horse genome is now well mapped and includes approximately 1.5 million single nucleotide polymorphisms from a range of breeds. There are many examples of future prospects for gene therapy for diseases of companion and farm animals. In the field of inherited and acquired diseases, domestic animals are destined to increase in importance for testing genetic-based therapies. They may also themselves be the target for such therapies. Of the domestic species, the dog provides the most useful models of human disease and also provides a source of spontaneous diseases which can be used to assess gene therapies.

Transgenic rabbits, goats and sheep have been developed to synthesise potentially high value biopharmaceutical products. To date, success in this field of “pharming” has been limited. However, one product, recombinant human antithrombin III, has received regulatory approval. A future growth area is likely to be the introduction of transgenic cattle producing humanised polyclonal antibodies for the treatment of pathogens that mutate rapidly.

The development of resistance of bacteria and other microbes to the actions of antimicrobial drugs progresses inexorably and causes considerable concern. As Martinez and Silley indicate, “the global impact of a shrinking therapeutic arsenal has precipitated numerous efforts to track the emergence and prevalence of resistance”.

In veterinary medicine, those responsible for the development, licensing, and therapeutic use of antimicrobial drugs have to consider not only the problems relating to ineffective treatment of microbial-based infectious diseases in animals but also the possibly overstated concern arising from the transfer of resistance from animals (or animal food products) to man. Martinez and Silley review all aspects of resistance with emphasis on underlying mechanisms, monitoring programmes, and the impact of clinical use on its emergence and, in particular, with the pharmacokinetic concepts of mutation selection window and the integration of pharmacokinetic and pharmacodynamic data to provide indices, such as $C_{max}:MIC$ and $AUC:MIC$ ratios and $T > MIC$, which are widely used as a rational basis for selecting doses designed to minimise opportunities for the emergence of resistance. The mechanisms of resistance emergence at the molecular level are many but all involve an alteration to proteins synthesised by bacterial cells. The definition of resistance is no simple matter; bacteriologists, pharmacologists, epidemiologists, and clinicians all have their views. There is the added consideration of distinguishing between resistance and tolerance. In this chapter the key consideration has been to consider the innumerable factors which may contribute to resistance and the importance of

selecting dosages which minimise its emergence. The role and importance of biofilms and quorum sensing signalling systems between bacterial cells are also reviewed, as is the role in eradicating bacteria of the immunomodulatory and anti-inflammatory actions on the host exhibited by some classes of antimicrobials.

The therapeutic use of drugs in food producing animal species may lead to residues of drugs and their metabolites. Drug residues in edible fluids and tissues of food-producing animals have become an issue of major public health concern and are now consequently a major consideration in the licensing of drug products for veterinary use. Drug residues comprise a major link between veterinary therapeutics and the health of humans. Reeves outlines the framework for undertaking the food safety risk analysis. This involves four components: hazard identification, hazard characterisation, exposure assessment, and risk characterisation. Dietary risk is defined by the relationship, $\text{risk} = \text{hazard} \times \text{exposure}$, where risk is the probability of harm for the consumer, hazard is the chemical residue (drug and/or metabolite) in edible tissue and exposure is the dietary exposure of the residue.

As yet, there is no harmonisation at international level governing how residues of drugs and their metabolites should be regulated. However, the guidelines of many jurisdictions work on the principle of maximum residue limits (MRLs) which are set on the basis of a no observable effect level (NOEL), usually defined in laboratory animal chronic toxicology studies, but also involving other possible data sources. This is then translated, using an appropriate safety factor, into an amount of drug plus metabolite residue, which can be consumed daily by humans over a lifetime without causing appreciable risk to human health, the Acceptable Daily Intake (ADI). Some regulatory authorities distinguish between the risks associated with short-term acute toxicity and consumption over a lifetime, enshrined in concepts such as acute reference dose (ARfD). The exposure assessment is on the basis of consumption daily of an assumed diet.

Following risk assessment, regulatory authorities undertake risk management procedures, the essential element of which is setting a withdrawal time, which is the time between last administration of product and the time when an animal can be safely slaughtered for food. Compliance with the withdrawal period is required to provide assurance on safety and there are therefore in place residue surveillance programmes. As well as ensuring consumer safety, drug residues legislation and testing is an important facilitating element in international trade of animal derived foodstuffs. There are several future challenges in relation to residues. They include the need for international harmonisation and close liaison between producers of drug products, regulators and surveillance assessors.

Boxall discusses the release of drugs and their metabolites into the environment and the impact this may have on wildlife, insects, etc., arising from the use of veterinary medicines (both legally and non-legally). The classical example of chemical impact on, and persistence in, the environment is DDT, not a veterinary medicine but a pesticide which, nevertheless, was shown to have a devastating impact on many species of wildlife (notably birds). Companies marketing veterinary medicines are required by regulatory authorities to undertake not only edible tissue residue studies but also environmental risk assessments. This is required to

provide assurance that the impact of veterinary medicinal products and their metabolites on aquatic and terrestrial organisms (including man) is absent, negligible, or at the very least acceptable.

Entry into the environment may arise in several ways; for example, during the manufacturing process, but more commonly from excreta discharged into the environment following livestock treatment and use in aquaculture. Following entry into the environment, the fate of drugs {and their metabolites} should be established in several ways, namely the initial sorption into soil, and then the subsequent persistence in and transport within soil systems. The latter requires data to establish leaching to ground water, run off, and drainflow. Other aspects of fate of excreted drugs and their metabolites include the presence in surface waters and the uptake by biota.

There is finally the question of impact of discharged veterinary residues on the environment, including the possibility of risks to human health. Human exposure can potentially occur through crop consumption or through contaminated ground and surface waters. Estimates of exposure through these indirect routes (as opposed to the direct exposure through consumption of food from treated animals) have, to date, given reassurance on risks to human health.

The environmental impact on non-human organisms is established in studies required by regulatory authorities, and effects are generally classified as chronic or subtle. This chapter cites three classic examples of why vigilance is required in monitoring and assessing the environmental impact of veterinary residues: avermectins and terrestrial and aquatic vertebrates; antimicrobial drugs and soil dwelling microorganisms; and diclofenac and the fate of vultures. The veterinary (but generally non-licensed) use of the NSAID, diclofenac, to treat cattle in India and Pakistan provides an especially dramatic example of the potential hazards to human health. Subsequent vulture feeding on contaminated carcasses led to large scale deaths of the birds through renal failure and visceral gout, thus leading to a decline in the populations. Carcasses are also consumed by feral dogs and as the vulture population has declined the feral dog population has risen. It may be noted that feral dogs are a main source of rabies in India. An estimate has been given of thousands of human deaths through this sequence of events.

Doping as an important aspect of abuse of drugs is of major concern in both human and veterinary sports medicine. It involves the illegitimate use of drugs or any compound with pharmacological activity with a view to altering (enhancing or diminishing) performance. Anti-doping policy is designed to prevent such use of such substances. Several veterinary species are involved in competitive sports and the use of drugs to modify performance is therefore a concern, primarily in all equine competitive sports and dog racing but also, perhaps less obviously, in camel racing and even in bull fighting in some countries. Toutain deals with pharmacological, performance and control issues, relating especially to the horse. There is the key issue of medication versus doping control, between which a clear distinction must be made, as medication is given for the benefit of the animal and withholding drugs required for therapeutic reasons might be unacceptable on welfare grounds.

Once the use of drugs in doping has been clearly identified, there is in place a sophisticated set of procedures and principles for decision taking, which is now operative, at least in relation to the horse. The detection and quantitation of illegal substances is based on sensitive methods of analysis (usually GC-MS or LC-MS) of biological fluids, such as urine and plasma, the results of which are linked to pharmacological considerations of drug potency. The key question is, is it possible to select a breakpoint concentration of active drug which is low enough to guarantee that, despite its detection and quantitation at low concentrations, pharmacological actions will not be exerted to a degree that would alter performance? This is the scientifically acceptable alternative to what has been called “the zero tolerance rule”. This new approach attempts to define for each drug an irrelevant urine or plasma concentration, on the basis of pharmacokinetic/pharmacodynamic principles which allows for the detection of therapeutically useful drugs in low concentration. Nevertheless, the zero tolerance rule still applies to compounds which do not have any defined therapeutic uses in the horse. For therapeutic agents, guidance (based on pharmacokinetic principles) is offered to stakeholders on the duration of detection time in plasma or urine following administration of a clinically recommended dose. This duration comprises a withdrawal time before competing. For some drugs and some jurisdictions, there are permitted levels of drugs which do not have to meet the requirement of irrelevant plasma or urine concentrations.

Currently, the major challenges in horse doping control relate to the scientific basis for limiting the illegal use of recombinant biological substances, such as erythropoietin and growth hormone, with potentially long-lasting effects, while parent compounds are not detectable for more than several days. Innovative bioanalytical approaches, using molecular tools, are now being developed to address these issues. The application of proteomic and metabolomic techniques will be used, among others, to address current and future challenges.

The main matrix currently in use for analysis is urine. Actually, plasma is a more robust matrix but is generally not used for practical reasons. The use of faeces and hair (mane or tail) have also been proposed; the latter is of interest as it provides a stable bioenvironment, in which drugs have been identified and quantified years after their administration. In pigeon racing, faeces (actually a mixture of urine and faeces) are the matrix used. Finally, it is to be hoped that increasing levels of international harmonisation will be reached on veterinary doping issues. There are current differences between jurisdictions.

In summary, this volume contains a series of chapters that can each stand alone as a state of the art review but which also, together, serve to illustrate current knowledge of key topics in the speciality of veterinary pharmacology and how the discipline links to, and interfaces with, that of human pharmacology.

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Species Differences in Pharmacokinetics and Pharmacodynamics

Pierre-Louis Toutain, Aude Ferran, and Alain Bousquet-Mélou

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Abstract Veterinary medicine faces the unique challenge of having to treat many types of domestic animal species, including mammals, birds, and fishes. Moreover, these species have evolved into genetically unique breeds having certain distinguishable characteristics developed by artificial selection. The main challenge for veterinarians is not to select a drug but to determine, for the selected agent, a rational dosing regimen because the dosage regimen for a drug in a given species may depend on its anatomy, biochemistry, physiology, and behaviour as well as on the nature and causes of the condition requiring treatment. Both between- and within-species differences in drug response can be explained either

P.-L. Toutain (✉), A. Ferran, and A. Bousquet-Mélou

Unité Mixte de Recherche 181 Physiopathologie et Toxicologie Expérimentales, Institut National de la Recherche Agronomique et Ecole Nationale Vétérinaire de Toulouse, 23 Chemin des Capelles, BP 87 614, 31076 Toulouse cedex 03, France

e-mail: pl.toutain@envt.fr; a.ferran@envt.fr; a.bousquet-melou@envt.fr

by variations in drug pharmacokinetics (PK) or drug pharmacodynamics (PD), the magnitude of which varies from drug to drug. This chapter highlights selected aspects of species differences in PK and PD and considers underlying physiological and patho-physiological mechanisms in the main domestic species. Particular attention was paid to aspects of animal behaviour (food behaviour, social behaviour, etc.) as a determinant of interspecies differences in PK or/and PD. Modalities of drug administration are many and result not only from anatomical, physiological and/or behavioural differences across species but also from management options. The latter is the case for collective/group treatment of food-producing animals, frequently dosed by the oral route at a herd or flock level. After drug administration, the main causes of observed inter-species differences arise from species differences in the handling of drugs (absorption, distribution, metabolism, and elimination). Such differences are most common and of greatest magnitude when functions which are phylogenetically divergent between species, such as digestive functions (ruminant vs. non-ruminant, carnivore vs. herbivore, etc.), are involved in drug absorption. Interspecies differences also exist in drug action but these are generally more limited, except when a particular targeted function has evolved, as is the case for reproductive physiology (mammals vs. birds vs. fishes; annual vs. seasonal reproductive cycle in mammals; etc.). In contrast, for antimicrobial and antiparasitic drugs, interspecies differences are more limited and rather reflect those of the pathogens than of the host. Interspecies difference in drug metabolism is a major factor accounting for species differences in PK and also in PD (production or not of active metabolites). Recent and future advances in molecular biology and pharmacogenetics will enable a more comprehensive view of interspecies differences and also between breeds with existing polymorphism. Finally, the main message of this review is that differences between species are not only numerous but also often unpredictable so that no generalisations are possible, even though for several drugs allometric approaches do allow some valuable interspecies extrapolations. Instead, each drug must be investigated on a species-by-species basis to guarantee its effective and safe use, thus ensuring the well-being of animals and safeguarding of the environment and human consumption of animal products.

Keywords Pharmacokinetics · Pharmacodynamics · Species variation · Drug administration · Drug disposition

1 Introduction

Veterinary medicine faces the unique challenge of having to treat many types of animals, including livestock, companion animals, working animals, sports animals, laboratory animals, and some invertebrates such as honeybees. Most are domesticated species, but exotic animal species are also kept as pets (reptiles, amphibians, birds) and may therefore require treatment. In veterinary medicine, the main

challenge is not to select a drug but rather to determine, for the selected agent, a rational dosing regimen (involving dose rate, inter-dosing interval, duration of treatment and modalities of administration), because the dosage regimen for a drug in a given species may depend on its anatomy, biochemistry, physiology, and behaviour, as well as on the nature and causes of the condition requiring treatment. Hence, major biological differences impacting on dosage exist between animal species. In addition, within some species there may be considerable differences within and between breeds in pharmacokinetic (PK) and pharmacodynamic (PD) profiles; veterinary pharmacogenetics is a new branch of veterinary science which aims to identify genetic variations (polymorphisms) as the origin of differences in the drug response of individuals within a given species. These between- and within-species differences in drug response are largely explained by variations in drug PK and PD, the magnitude of which varies from drug to drug.

This chapter highlights selected aspects of species differences in PK and PD and that considers underlying physiological and patho-physiological mechanisms in the main domestic species for which a useful review has been published (Baggot and Brown 1998). A text book (Baggot 2001) entitled “*The physiological basis of veterinary clinical pharmacology*” provides numerous examples of interspecies differences in drug disposition and effects together with their physiological basis. Questions relating to zoological pharmacology have recently been reviewed (Hunter 2009) and will not be covered in this chapter.

2 Diversity of Species and Breeds of Interest for Veterinary Medicine

There are more than 40 domestic livestock species. The World Watch List for Domestic Animal Diversity [WWL-DAD:3; (FAO 2000)] issued by FAO provides inventories of the species and breeds of the domestic animals used for food production. Of this number, 13 species contribute to most of the world's food and agricultural production and are of veterinary interest. The evolutionary inter-relationships and population size of these domestic mammalian and avian species are summarised in Fig. 1. Some species are classified as major and others as minor species by the regulatory agencies in Europe and the US (Table 1). It should be stressed that some species classified as minor by Western country scientists, such as buffaloes and goats, have a worldwide population large enough to confer a status of “major” species on such animals. For example, there are about 150 million buffaloes and 800 million goats in the world. The physiological characteristics of these different species reflect adaptations that have evolved over the last millennia, not only to promote their survival in local environments but also as a consequence of their usage by man. This explains why these 13 predominant species have evolved into genetically unique breeds. A breed is defined as a group of animals having common ancestry and certain distinguishable characteristics developed by artificial selection and maintained by controlled propagation (Fleischer et al. 2008).

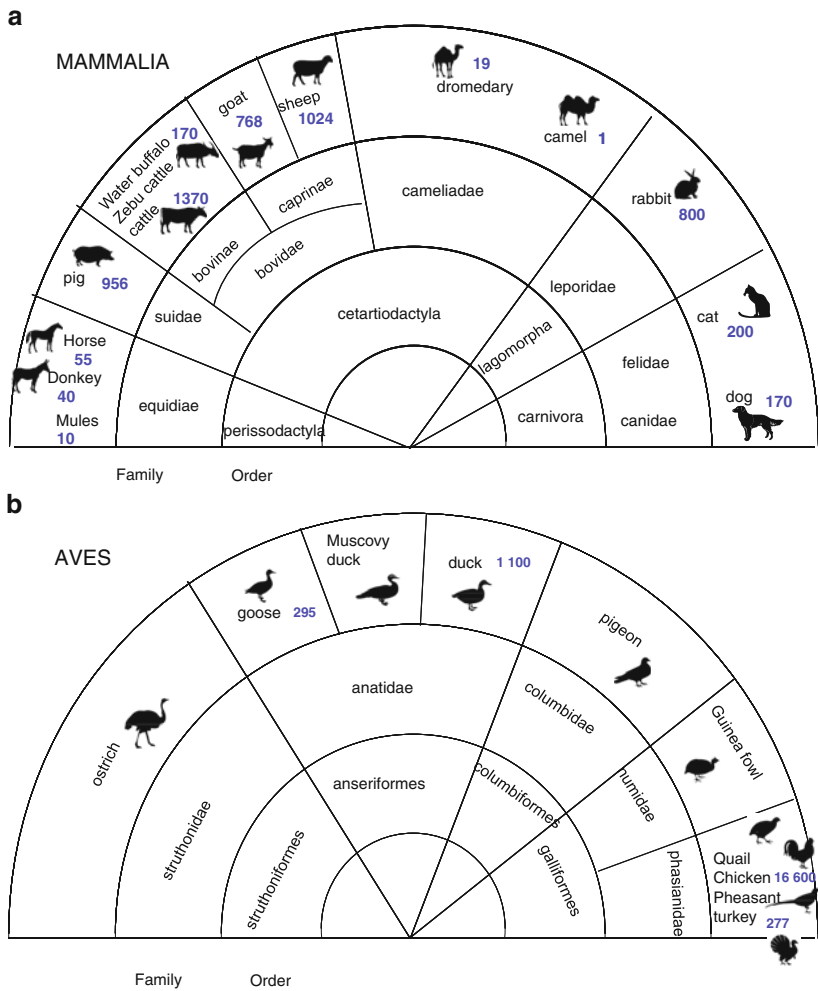


Fig. 1 (a, b): Species of veterinary interest with the worldwide size ($\times 10^6$)

For domestic species, about 400 of the 6,000 identified breeds are of economic relevance for meat, milk, and egg production.

Dogs were the first animal species to be domesticated and subsequently they have been selectively bred for thousands of years. This has resulted in a wide variety of more than 400 breeds worldwide with differing anatomical, physiological, and behavioural traits. Consequently, it can be inappropriate to generalise PK and PD drug properties to “the dog”. For example, certain dog breeds carry a mutation in the ATP-binding cassette (ABC) gene ABCB1, encoding for the efflux transporter P-glycoprotein (PgP). This results in impairment in the barrier function of the blood–brain barrier with the result that these animals are more sensitive to

Table 1 Major and minor species (EMA/CVMP 2003) in the EU and the USA

Major food-producing species for MRLs	Cattle (dairy, meat animals) Sheep (meat animals) Pigs Chicken (including laying hens) Turkey (USA but not EU) Salmonidae
Major non-food-producing animals	Cats Dogs
Minor food-producing species for MRLs	Other ruminants (bovidae including caprinae and their milk, deer, reindeer) Sheep (dairy) Other avian species and their eggs Other fish species Other mammalian species (horse, rabbit, dromedary) Honey bees
Minor non-food-producing species (distinguished from wildlife, exotic species in the USA)	All other species used as pets

certain antiparasitic agents, such as the ivermectins, and to morphine derivatives, such as loperamide. The dog is the first species for which genotyping was performed to select (or to avoid) drugs that are substrates of PgP (Mealey 2009). There is much less genetic diversity in cats, because they have been domesticated more recently and they were not selected for purposes other than to be a “home” animal.

Recent selection processes have accelerated the development of diversity within the most productive breeds, leading to the creation of distinct strains primarily in high input systems such as for poultry and also for laboratory animals (dogs, rodents). Strains are an artificially created variety of descendants from a common ancestor that have been developed with the aim of improving some special morphological or behavioural characteristics, or enhanced performance. This is not without consequences for the PK and PD properties of drugs. For example, it has been shown that the plasma clearance of celecoxib, a selective cyclooxygenase (COX)-2 inhibitor, can be 2.5-fold higher in some strains of beagle dogs than in others (Paulson et al. 1999). This is of major concern because beagle dogs are usually selected for regulatory purposes as the model breed in pre-clinical trials to determine the initial drug dosage regimen in dogs.

The multiplicity of species of veterinary interest with their large interspecies differences in PK and PD prompted a generation of pharmacologists to attempt to establish some universal “law” or, more modestly, to develop some modelling tools to extrapolate PK and even PD parameters between species. Allometry is one of these systematic approaches; it is the study across species of the influence of body size on the numerical values of PK or PD parameters. Allometry may be useful in drug development to provide a first estimate of a dosage regimen but it is only usefully predictive if the differences between animal species are of a quantitative rather than a qualitative nature. Most drugs are not scalable across multiple species (Riviere et al. 1997) and there can be no replacement for experimental PK data. The same