The Physiological Basis of Veterinary Clinical Pharmacology

J. Desmond Baggot, MVM, PhD, DSc, FRCVS

Formerly Professor of Preclinical Veterinary Studies, Faculty of Veterinary Science, University of Zimbabwe, Harare and Professor of Clinical Pharmacology, School of Veterinary Medicine, University of California, Davis.

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Preface

Material for this monograph has been collected over the past 25 years. The book is, in some respects, an update of *Principles of Drug Disposition in Domestic Animals* which was published in 1977, but it is more broad in scope. References to selected pre-1975 papers are included because of their inherent value.

The diversity of species in which drugs are used for clinical purposes together with the emphasis placed on the various classes of drugs distinguishes veterinary from human pharmacology. Physiological characteristics of different species essentially reflect adaptations that evolved over centuries to promote survival of the existing species. Even though each species is unique, the pattern of most physiological processes in the species within a taxonomical class can be described in mathematical terms. Species differences in the response to fixed doses or dosage regimens of drugs generally have a physiological or biochemical basis. An uncharacteristic response to dosage of a drug in animals of a particular species often warrants investigative research on the underlying mechanism to which the observed effect could be attributed.

Pharmacokinetic parameters are most useful for quantifying species differences in the bioavailability and disposition of drugs, and for calculating therapeutic dosage regimens. An assumption made in dosage calculations, which appears to be generally valid, is that the same range of therapeutic plasma concentrations is applicable to eutherian mammalian species. Disease states and pharmacokinetic-based drug interactions can alter the disposition of a drug to an extent that modification of usual dosage is required for safety and efficacy of the drug. The formulation of dosage forms determines not only the route of administration but also the clinical efficacy of a drug. Because residues of drugs and drug metabolites in the tissues and edible products of food-producing animals are unacceptable, drugs should be formulated as preparations that will be efficacious and will not prolong the persistence of residues. In formulating veterinary dosage forms, meagre consideration has been given to differences in the pharmacodynamic activity and to species variations in the bioavailability and disposition of the enantiomers of chiral drugs. Application of interspecies allometric scaling of major pharmacokinetic parameters is useful at the pre-clinical stage of drug development and may identify non-conforming species with regard to the disposition of commercially available drugs. It is well established that drug dosage cannot be extrapolated between different classes of animals (mammals, birds, fishes, reptiles). At the present

time there is insufficient information available on the pharmacodynamic activity and pharmacokinetic behaviour of drugs in marsupial species to comment on the feasibility of extrapolating dosage from eutherian to marsupial mammals. The conservation of exotic animals requires protection of their natural habitats from human intrusion as the various adaptations that characterize different species have evolved in concert with their habitats.

Veterinary clinical pharmacology is an integrative discipline with the general objective of providing the requisite information for judicious selection of drug preparations for use in animals at dosages that will alleviate discomfort and pain, avoid undesirable drug interactions and effectively treat animal diseases. The specific aim of drug therapy is to readjust disease-altered physiological and/or biochemical processes to the state that is normal for the animal species. The author hopes that this book will promote postgraduate research that will both contribute to advancement of veterinary clinical pharmacology and further the well-being of animals.

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Terms and Abbreviations

ACE	angiotensin-converting enzyme
AChE	acetylcholinesterase
AUC_{0-24}	area under the concentration-time curve measured from t = 0 to t = 24 h
AUIC	area under the inhibitory plasma concentration – time curve (with reference to antimicrobial agents)
AUMC	area under the first moment of the plasma concentration – time curve, i.e. the area under the curve of the product of time and plasma concentration over the time-span zero to infinity
b.d.	twice daily
BSP	bromosulphalein
BUN	blood urea nitrogen
C_{max}	maximum concentration of a drug
CK	creatine kinase
Cl	clearance (L/h or mL/min)
D	dose (mg)
DDT	dichlorodiphenyl-trichloroethane
DEET	diethyltoluamide
E	extraction ratio
E_H	hepatic extraction ratio
ED_{50}	median effective dose (mg/kg)
F	systemic availability (extent of absorption)
f_b	fraction of bound drug
f_u	fraction of unbound drug
FMO	flavin-containing mono-oxygenase
GABA	γ-aminobutyric acid
GFR	glomerular filtration rate
HPLC	high performance liquid chromatography
IBR	infectious bovine rhinotracheitis
ICG	indocyanine green
i.m.	intramuscular
i.o.	intraosseous
i.p.	intraperitoneal
i.v.	intravenous
k_a	absorption rate constant

k_d	disposition rate constant
K_M	Michaelis constant
LD_{50}	median lethal dose (mg/kg)
LOQ	limit of quantification
M	molar
MAT	mean absorption time
MIC_{90}	minimum inhibitory concentration required to prevent visible growth of 90% of a bacterial species *in vitro*
MLP	maximum life-span potential
MRT	mean residence time
n	number
NS	not significant
NSAIDs	non-steroidal anti-inflammatory drugs
OTC	oxytetracycline
OTC-C	conventional oxytetracycline
OTC-LA	long-acting oxytetracycline
P	probability
P_{Cr}	creatinine concentration in plasma
PASME	post-antibiotic sub-minimum inhibitory concentration effect
PCB	polychlorinated biphenyl
PCV	packed cell volume
pH	negative logarithm of the hydrogen ion concentration
pK_a	negative logarithm of the acidic ionization/dissociation constant
p.o.	*per os* (by mouth)
p.r.	*per rectum* (rectal administration)
Q	blood flow (L/h)
R_0	infusion rate required to produce steady-state plasma concentration
s.c.	subcutaneous
SD	standard deviation
SEM	standard error of the mean
t	time
$t_{\frac{1}{2}}$	half-life (i.v. administration of a drug)
U_{Cr}	creatinine concentration in urine
V	total volume of urine formed during collection period
$V_{d(area)}$	volume of distribution (L)
$V_{d(ass)}$	volume of distribution at steady-state (L)
V_{max}	maximum reaction velocity
α	absorption-rate constant
β	elimination-rate constant
β-agonists	
β-antagonists	

Author's Note

The values of pharmacokinetic terms for drugs mentioned in this monograph are average values in the various animal species, while drug doses and dosage regimens are based on average values and agree reasonably well with those usually recommended. Some emphasis is placed on veterinary dosage forms since they influence the clinical efficacy of drugs to a greater degree than is generally appreciated. Advancement of veterinary clinical pharmacology rests both on elucidating the physiological and/or biochemical basis of species variations in response to dosage of drugs and on the development of dosage forms that will most effectively deliver the drugs to their sites of action without producing adverse effects. Keen observation and attention to detail are requirements of animal management in general and of veterinary clinical pharmacology in particular.

Chapter 1

The Pharmacokinetic Basis of Species Variations in Drug Disposition

Introduction

The diversity of species in which drugs are used and studied distinguishes veterinary from human pharmacology. Another difference, which relates to clinical indications, is the emphasis placed on the various classes of drugs.

An understanding of the complex relationship between the dose of a drug and the clinically observed pharmacological effect can generally be obtained by linking the pharmacokinetic (PK) behaviour with information on pharmacodynamic (PD) activity (Fig. 1.1) (Holford & Sheiner, 1981).

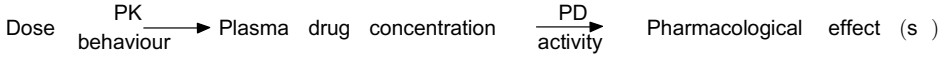

Fig. 1.1 Schematic representation of the dose–effect relationship.

The plasma drug concentration profile occupies a central role between the dose administered and the characteristic pharmacological effect(s) produced by the drug. An inherent assumption is that the drug concentration in plasma is related to the concentration at the site of action, which can rarely be measured *in vivo*. The requirement for species differences in the dose (mg/kg) or dosage rate (dose/dosage interval) of a pharmacological agent may be attributed to variation between species in pharmacokinetic behaviour or pharmacodynamic activity, or both, of the drug. Whether a systemically acting drug produces a therapeutic or toxic effect is mainly determined by size of the dose when a single dose is administered or the dosage rate when multiple doses are administered at a constant dosage interval.

Drugs (pharmacological agents) act by modifying pre-existent physiological or biochemical processes in the body. The mechanisms of action of drugs appear to be the same in mammalian species. The clinical utility of pharmacokinetics relies on the premise that a range of therapeutic plasma concentrations can be defined for each pharmacological agent; some examples are given

in Table 1.1. The pharmacodynamic properties (affinity and efficacy) of a drug are embodied in the therapeutic concentration range. There is substantial evidence to support the hypothesis that the therapeutic concentration range is the same for human beings and domestic animals. The calculation of a dosage regimen (dose and dosage interval) for a drug preparation is based upon a knowledge of the therapeutic concentration range and the pharmacokinetic parameters that describe bioavailability and disposition of the drug. Species differences in the dosage regimen for a drug preparation can generally, but not always, be attributed to variation between species in pharmacokinetic behaviour of the drug.

Table 1.1 Principal pharmacological effect and range of therapeutic plasma concentrations of some drugs.

Drug	Pharmacological effect	Therapeutic concentrations
Quinidine	Anti-arrythmic	2–6 μg/mL
Procainamide	Anti-arrythmic	6–14 μg/mL
Lignocaine (lidocaine)	Anti-arrythmic	1.5–5 μg/mL
Propranolol	Anti-hypertensive	20–80 ng/mL
Verapamil	Anti-arrythmic	80–320 ng/mL
Digoxin	Positive inotropic	0.6–2.4 ng/mL
Phenobarbitone	Anticonvulsant	10–25 μg/mL
Pethidine (meperidine)	Analgesic	0.4–0.7 μg/mL
Theophylline	Bronchodilator	6–16 μg/mL

Plasma concentration profile

Following the administration of a single dose of a drug preparation (dosage form), the factors that influence the plasma drug concentration profile include: the size of the dose (mg/kg), the formulation and route of administration of the drug preparation, the extent of both plasma protein binding and extravascular (tissue) distribution, and the rate of elimination (which refers to biotransformation and excretion) of the drug. The significant variable associated with oral, intramuscular or subcutaneous administration, namely bioavailability (i.e. the rate and extent of drug absorption into the systemic circulation), can be discounted by administering the drug intravenously as a parenteral solution (if available). It is only when a drug is administered intravenously that complete systemic availability (100% absorption of the dose) can be assumed.

Some intravenous anaesthetic agents

Pharmacokinetic studies of intravenous anaesthetic agents provide useful information for comparative purposes. Following the intravenous injection of a

single dose (25 mg/kg) of pentobarbital sodium to goats and dogs, the plasma concentration–time curves (plotted on arithmetic coordinates, Fig. 1.2) show that the various reflexes return and the animals of both species awaken from anaesthesia at the same plasma pentobarbitone concentrations, but at widely different times after drug administration (Davis *et al.*, 1973). The difference in the duration of anaesthetic effect is related to species variation in the rate of biotransformation (hepatic microsomal oxidation) of pentobarbitone.

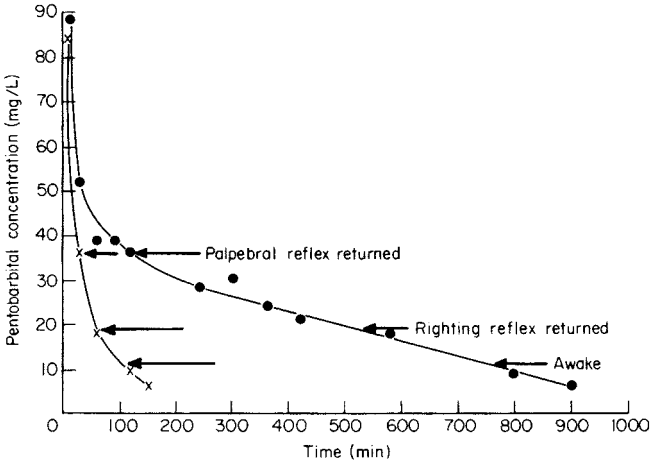

Fig. 1.2 Curves showing the decline in plasma concentrations of pentobarbital in goats (x⟷x) and dogs (●⟷●) following the intravenous injection of a single dose (25 mg/kg) of pentobarbital sodium. Arrows indicate the plasma pentobarbital concentrations (and related times) at which the various reflexes return and the animals of both species awaken from anaesthesia. (Reproduced with permission from Davis *et al.* (1973).)

The systemic clearance and the half-life of thiopentone, administered as an intravenous bolus dose, significantly differ between sheep and dogs. However, both species, as well as cats and human beings, awaken from anaesthesia at the same plasma thiopentone concentration (20 μg/mL). It is mainly redistribution of thiopentone from the highly perfused tissues (including the central nervous system (CNS)) to less well perfused tissues (such as skeletal muscle) and ultimately body fat, rather than elimination by hepatic biotransformation, that determines the duration of anaesthetic effect (Fig. 1.3) (Brodie *et al.*, 1952). Compared with mixed-breed dogs, Greyhounds and probably other lean breeds of hound (such as Whippet, Saluki and Afghan) recover more slowly from thiobarbiturate (thiopental and thiamylal) induced anaesthesia and show intermittent struggling and relapses into sleep during the recovery period. The slower and less smooth recovery of Greyhounds may be largely attributed to the lower body fat content, as a percentage of body weight, and partly to slower dose-dependent hepatic biotransformation of thiobarbiturates. Between 2 and 8 h after intravenous administration, the plasma concentrations of thiopental

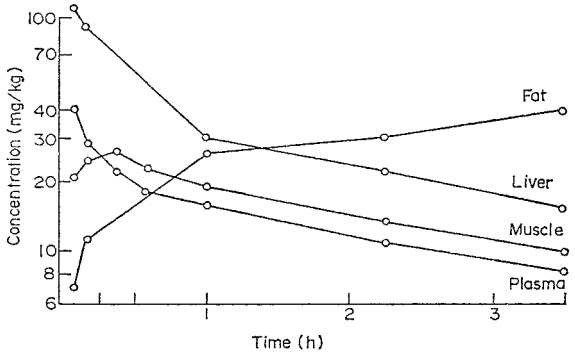

Fig. 1.3 Concentrations of thiopentone in various tissues and plasma of a dog after the intravenous administration of 25 mg/kg. (Reproduced with permission from Brodie *et al.* (1952).)

and thiamylal are significantly higher in Greyhounds than in mixed-breed dogs (Fig. 1.4) (Sams *et al.*, 1985). Premedication with acepromazine (0.25 mg/kg, i.m.) generally delays the time of awakening from thiopentone anaesthesia, although there is wide individual variation (Baggot *et al.*, 1984). The delayed awakening may have a pharmacodynamic rather than pharmacokinetic basis, or could be due to the sedative effect of the acepromazine.

Propofol, a highly lipophilic intravenous anaesthetic, rapidly induces anaesthesia of ultra-short duration in goats, dogs and human beings. Both redistribution and biotransformation of the drug contribute to the brief duration of anaesthetic effect. Even though the disposition kinetics of propofol differ among species and between mixed-breed dogs and Greyhounds (Zoran *et al.*, 1993), the blood propofol concentration at which dogs and seemingly goats return to the sternal position and human beings regain consciousness appears to be the same (1 μg/mL). The systemic clearance, expressed as mL/min·kg, of propofol exceeds hepatic blood flow in all species, particularly in goats (*vide infra*, Table 1.14). It can be concluded that another organ (the lungs) or extrahepatic tissue contributes to the metabolism, which takes place by conjugation reactions (glucuronide and sulphate synthesis), of propofol.

Ketamine, a dissociative anaesthetic, is administered as a racemic mixture (present in the parenteral preparation) and is initially metabolized by the liver to *N*-desmethylketamine (metabolite I), which in part is converted by oxidation to the cyclohexene (metabolite II) (Fig. 1.5). The major metabolites found in urine are glucuronide conjugates that are formed subsequent to hydroxylation of the cyclohexanone ring. As the enantiomers differ in anaesthetic potency and the enantioselectively formed (metabolite I has approximately 10% activity of the parent drug) interpretation of the relationship between the anaesthetic effect and disposition of ketamine is complicated. On a pharmacodynamic basis, the *S*(+) enantiomer is three times as potent as the *R*(−) enantiomer (Marietta *et al.*, 1977; Deleforge *et al.*, 1991), while the enantiomer that undergoes *N*-demethylation (hepatic microsomal reaction) differs between species (Delatour *et al.*, 1991). Based on the observed minimum anaesthetic

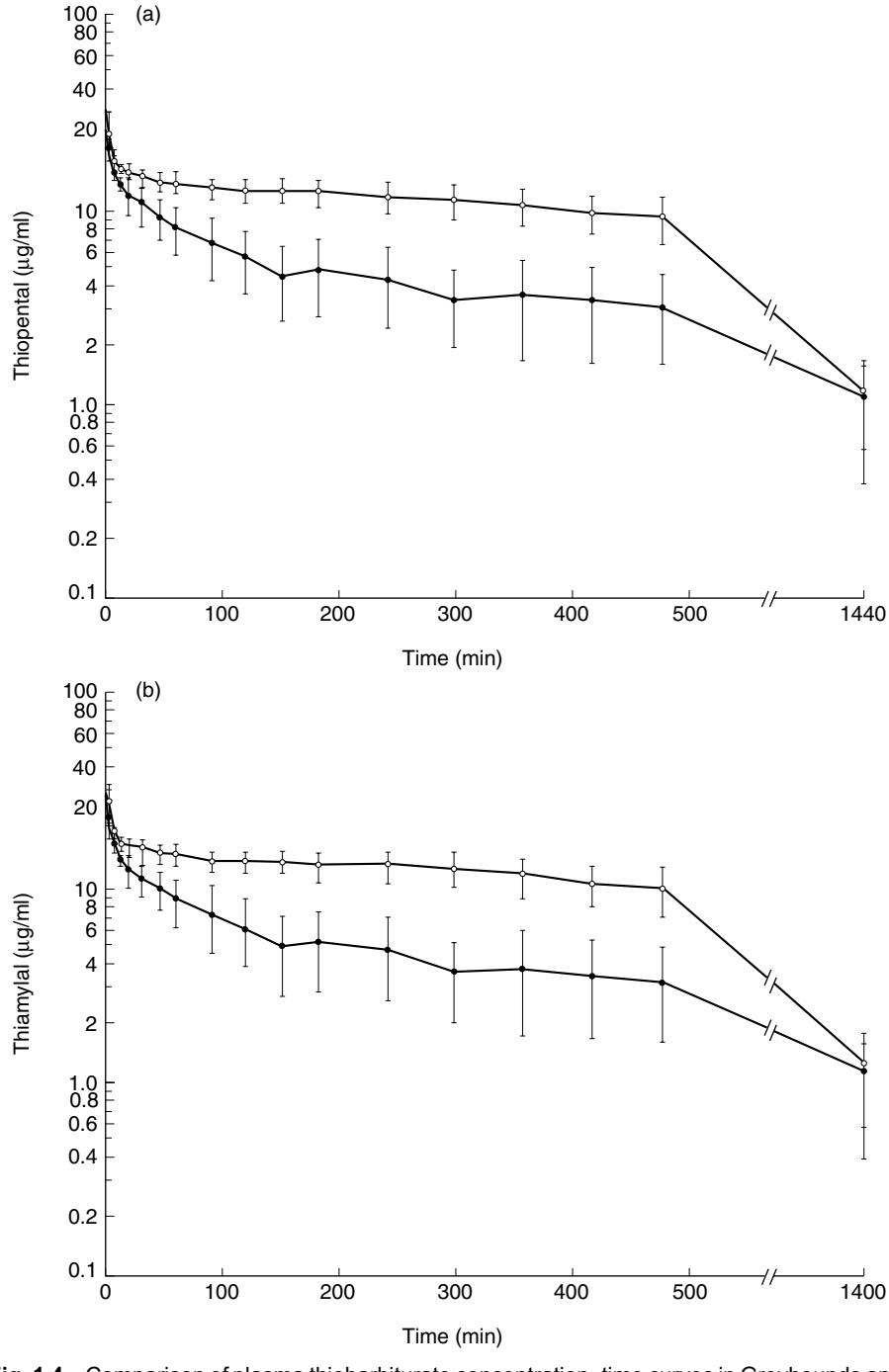

Fig. 1.4 Comparison of plasma thiobarbiturate concentration–time curves in Greyhounds and mixed-breed dogs following the intravenous administration of single doses (15 mg/kg) of thiopental and thiamylal (a) —Plasma thiopental concentrations in Greyhound (○—○) and mixed-breed dogs (●—●) after being given 15 mg of thiopental/kg, iv; mean ± SD. (b) —Plasma thiamylal concentrations in Greyhound (○—○) and mixed-breed dogs (●—●) after being given 15 mg of thiamylal/kg, iv; mean ± SD. (Reproduced with permission from Sams *et al*., (1985).)

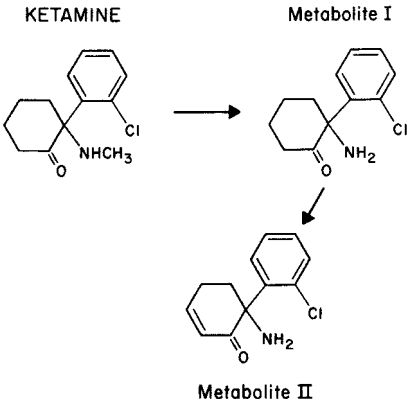

Fig. 1.5 Initial biotransformation (oxidative reactions) of ketamine. Both the parent drug and, to a lesser extent (10%), metabolite I are pharmacologically active.

concentration of ketamine in plasma (2 μg/mL), the duration of anaesthesia produced by a single intravenous dose relates mainly to distribution and partly, depending on the size of the dose, to biotransformation of the drug. The half-life of ketamine is shorter in domestic animals (sheep, 0.5 h; horses, 0.7 h; cattle, 0.9 h; dogs, 1 h; cats, 1.1 h), apart from pigs (2.3 h), than in human beings (2.5 h).

Species variations in dosage

Low dose requirements (relative to dogs) of xylazine (α_2-adrenoceptor agonist) for cattle and morphine (mainly μ-opioid agonist) for cats may be attributed to higher sensitivity of receptor sites in the central nervous system of the susceptible species to these drugs (Table 1.2). Brahman cattle appear to be even more sensitive than other breeds of cattle to xylazine, while the sedative dose for Isle of Rhum red deer (off the west coast of Scotland), although similar to that for cattle (0.1–0.2 mg/kg, i.m.), is one-tenth of the sedative dose required for mainland red deer (Fletcher, 1974). In giraffes, xylazine should not be used alone but it could be used in conjunction with etorphine; whenever the use of etorphine is intended, the narcotic antagonist diprenorphine should be available for administration. Certain breeds of dog (notably, the Basset Hound, Great Dane and Irish Setter) appear to be susceptible to bloat, probably due to aerophagia, some hours after xylazine administration.

The idiosyncratic toxicity, manifested by neurological effects, shown by a subpopulation of (rough-haired) Collies to ivermectin ($\geqslant$ 100 μg/kg, p.o.) may be attributed to a breed-related compromised blood–brain barrier (Tranquilli *et al.*, 1989), since γ-aminobutyric acid receptors that mediate neurotransmission are confined to the CNS in mammalian species. The pharmacokinetic behaviour of ivermectin does not differ between 'ivermectin-sensitive' and