

Drug Disposition and Pharmacokinetics

From Principles to Applications

Stephen H. Curry

Professor of Pharmacology and Physiology, University of Rochester, USA

Robin Whelpton

Senior Lecturer, Queen Mary University of London, UK

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Contents

Preface	xvii
About the Authors	xxi
1 Chemical Introduction: Sources, Classification and Chemical Properties of Drugs	1
1.1 Introduction	1
1.1.1 Source of drugs	2
1.2 Drug nomenclature and classification	3
1.3 Properties of molecules	3
1.3.1 Decomposition of drugs	7
1.3.1.1 Hydrolysis	7
1.3.1.2 Oxidation	9
1.3.1.3 Photodecomposition	9
1.3.1.4 Racemization	9
1.4 Physicochemical interactions between drugs and other chemicals	9
1.4.1 Chemical bonding and interactions between molecules	10
1.4.2 Solubility	11
1.5 Law of mass action	11
1.5.1 Reversible reactions and equilibrium constants	11
1.5.1.1 Sequential reactions	12
1.5.2 Reaction order and molecularity	12
1.5.3 Decay curves and half-lives	13
1.5.3.1 First-order decay	13
1.5.3.2 Zero-order decay	14
1.5.3.3 Second-order decay	15
1.6 Ionization	16
1.6.1 Henderson–Hasselbalch equation	18
1.7 Partition coefficients	18
1.7.1 Effect of ionization on partitioning	19
1.8 Stereochemistry	20
1.8.1 Cis-trans isomerism	20
1.8.2 Optical isomerism	21
1.8.2.1 Absolute configuration	21
1.8.3 Importance of stereochemistry in pharmacology	21
Further reading and references	22
2 Drug Administration and Distribution	23
2.1 Introduction	23
2.2 Drug transfer across biological membranes	24
2.2.1 Passive diffusion	24
2.2.1.1 <i>pH</i> -partition hypothesis	25
2.3 Drug administration	26

2.3.1	Oral administration	26
2.3.1.1	Presystemic metabolism	27
2.3.1.2	P-Glycoprotein	29
2.3.1.3	Gastrointestinal motility and splanchnic blood flow	29
2.3.1.4	Food and drugs	30
2.3.2	Sublingual administration	31
2.3.3	Rectal administration	31
2.3.4	Intravenous and intra-arterial injections	31
2.3.5	Intramuscular and subcutaneous injections	31
2.3.6	Transdermal application	32
2.3.7	Insufflation	32
2.3.8	Inhalation	32
2.3.9	Other routes of administration	32
2.4	Drug distribution	33
2.4.1	Extent of distribution	33
2.4.1.1	Apparent volume of distribution	33
2.4.2	Mechanisms of sequestration	34
2.4.2.1	pH differences	35
2.4.2.2	Binding to macromolecules	35
2.4.2.3	Dissolution in lipids	35
2.4.2.4	Active transport	35
2.4.2.5	Special processes	35
2.4.3	Kinetics of distribution	35
2.4.3.1	Tissue distribution of thiopental	37
2.4.3.2	Tissue distribution of guanethidine	38
2.4.4	Tissue distribution: more modern approaches	39
2.4.4.1	Microdialysis	39
2.4.4.2	Autoradiography	40
2.4.4.3	Positron emission tomography (PET)	41
2.5	Plasma protein binding	42
2.5.1	Assessing protein binding	44
2.5.1.1	Equilibrium dialysis	45
2.5.1.2	Ultrafiltration	46
2.5.2	Molecular aspects of protein binding	46
2.5.2.1	Microcalorimetry	46
2.5.2.2	Fluorescence spectroscopy	47
2.5.2.3	Circular dichroism (CD)	48
2.5.2.4	Electron paramagnetic resonance spectroscopy (EPR)	49
2.5.2.5	Commentary	49
2.5.3	Pharmacological importance of binding to plasma proteins	49
2.6	Summary	50
	References and further reading	50
3	Drug Elimination	53
3.1	Introduction	53
3.2	Metabolism	53
3.2.1	Phase 1 metabolism	54
3.2.1.1	Cytochrome P450 superfamily	55
3.2.1.2	Other oxidases	56
3.2.1.3	Hydrolysis	57
3.2.1.4	Reductions	58
3.2.2	Examples of phase 1 oxidation	59

3.2.2.1	Oxidation of alcohols	59
3.2.2.2	Aliphatic and aromatic hydroxylations	59
3.2.2.3	Oxidative desalkylation	59
3.2.2.4	<i>N</i> - and <i>S</i> -oxidation	59
3.2.2.5	Oxidative deamination	61
3.2.2.6	Desulfuration	61
3.2.2.7	Combination of reactions	61
3.2.3	Miscellaneous reactions	62
3.2.4	Phase 2 metabolism	62
3.2.4.1	<i>D</i> -Glucuronidation	62
3.2.4.2	Sulfation	63
3.2.4.3	<i>N</i> -Acetylation	64
3.2.4.4	Methylation	64
3.2.4.5	Glycine conjugates	65
3.2.4.6	Conjugation with glutathione	65
3.2.5	Kinetics of metabolism	65
3.3	Excretion	67
3.3.1	Urine	67
3.3.1.1	Glomerular filtration	68
3.3.1.2	Active tubular secretion	68
3.3.1.3	Passive diffusion	68
3.3.1.4	Renal clearance	69
3.3.1.5	Effect of urine pH and flow rate	70
3.3.2	Biliary excretion	70
3.3.3	Expired air	71
3.3.4	Saliva	71
3.3.5	Stomach and intestine	73
3.3.6	Breast milk	73
3.3.7	Other routes of excretion	74
3.3.7.1	Sweat	74
3.3.7.2	Hair and nails	74
3.3.7.3	Genital secretions	75
3.3.8	Cycling processes	75
3.3.8.1	Enterohepatic cycling	75
3.3.8.2	Significance of cyclic processes	76
	References and further reading	76
4	Elementary Pharmacokinetics	77
4.1	Introduction	77
4.2	Single-compartment models	78
4.2.1	Systemic clearance	79
4.2.2	Why drugs have different elimination half-lives	80
4.2.3	Intravenous administration	81
4.2.3.1	Half-life	81
4.2.3.2	Area under the curve	83
4.2.4	Absorption	84
4.2.4.1	Area under the curve	85
4.2.4.2	Special cases: $k_a < \lambda$ and $k_a = \lambda$	86
4.2.4.3	Special case: lag time	87
4.2.5	Infusions	87
4.2.5.1	Zero-order input	88
4.2.5.2	Loading dose	89

4.2.6	Multiple doses	90
4.3	Non-linear kinetics	92
4.3.1	Phenytoin	93
4.3.2	Ethanol	94
4.4	Relationship between dose, onset and duration of effect	95
4.5	Limitations of single-compartment models	96
4.6	Summary	97
References and further reading		97
5	More Complex and Model Independent Pharmacokinetic Models	99
5.1	Introduction	99
5.2	Multiple compartment models	99
5.2.1	Intravenous injections	99
5.2.1.1	Concentrations in the peripheral compartment	101
5.2.1.2	Microconstants	102
5.2.1.3	Apparent volumes of distribution	103
5.2.1.4	Clearance	104
5.2.2	Absorption	105
5.2.3	Infusions	105
5.2.4	Multiple oral dosing	106
5.2.5	Concept of compartments	107
5.2.6	Relationship between dose and duration of effect	108
5.3	Curve fitting and choice of most appropriate model	110
5.3.1	Graphical solution: method of residuals	110
5.3.2	Iterative curve-fitting	111
5.3.2.1	Weighted-regression	111
5.3.2.2	Choice of model	112
5.3.3	Quality of the data	112
5.4	Model independent approaches	113
5.4.1	Calculation of V_{Area} and clearance	113
5.4.2	Statistical moment theory	114
5.4.2.1	Estimating AUMC	115
5.4.2.2	Example of application of SMT	116
5.5	Population pharmacokinetics	117
5.6	Summary	118
References and Further Reading		118
6	Kinetics of Metabolism and Excretion	121
6.1	Introduction	121
6.2	Metabolite kinetics	121
6.2.1	Basic concepts	121
6.2.2	Fraction of metabolite formed	124
6.2.3	More complex situations	125
6.2.4	Active metabolites	126
6.2.5	Effect of presystemic metabolism	127
6.2.6	Interconversion of drug and metabolite	128
6.3	Renal excretion	129
6.3.1	Kinetics of urinary excretion	129
6.3.1.1	Renal clearance	130
6.3.1.2	Effect of urine flow rate	131
6.3.2	Specific drug examples	132

6.3.2.1	Amphetamine	132
6.3.2.2	Ethanol	132
6.3.2.3	Fluphenazine	133
6.4	Excretion in faeces	134
	References and further reading	135
7	Further Consideration of Clearance, and Physiological Modelling	137
7.1	Introduction	137
7.2	Clearance <i>in vitro</i> (metabolic stability)	137
7.2.1	Microsomes	137
7.2.2	Hepatocytes	138
7.3	Clearance <i>in vivo</i>	139
7.3.1	Apparent oral clearance	140
7.3.2	Two-compartment models	140
7.3.3	Systemic clearance at steady-state	140
7.3.4	Additivity of clearance	141
7.4	Hepatic intrinsic clearance	141
7.4.1	Effect of plasma protein binding on elimination kinetics	143
7.4.1.1	Influence of protein binding on hepatic clearance	144
7.4.1.2	Influence of protein binding and volume of distribution on half-life	145
7.4.2	First-pass metabolism	146
7.5	<i>In vitro</i> to <i>in vivo</i> extrapolation	148
7.6	Limiting values of clearance	149
7.7	Safe and effective use of clearance	150
7.8	Physiological modelling	150
7.8.1	Practical considerations	152
7.9	Inhomogeneity of plasma	153
	References and further reading	154
8	Drug Formulation: Bioavailability, Bioequivalence and Controlled-Release Preparations	157
8.1	Introduction	157
8.2	Dissolution	158
8.3	Systemic availability	158
8.3.1	Effect of bioavailability on plasma concentration–time curves	159
8.4	Formulation factors affecting bioavailability	160
8.4.1	Origins of variation	160
8.4.1.1	Diluents	160
8.4.1.2	Granulating and binding agents	160
8.4.1.3	Lubricants and surfactants	160
8.4.1.4	Disintegrating agents	161
8.4.1.5	Miscellaneous	161
8.4.1.6	Coated tablets	161
8.4.1.7	Capsules	161
8.4.2	Examples of drugs showing bioavailability variations	161
8.5	Bioequivalence	165
8.6	Controlled-release preparations	165
8.7	Conclusions	167
	References and further reading	167
9	Factors Affecting Plasma Concentrations	169
9.1	Introduction	169

9.2	Time of administration of dose	170
9.2.1	Time of day, and association of dosing with meal times	170
9.3	Food, diet and nutrition	171
9.3.1	Physical interaction with food	171
9.3.2	Macronutrients	171
9.3.3	Micronutrients	172
9.4	Smoking	173
9.5	Circadian rhythms	173
9.5.1	Absorption	174
9.5.2	The liver	174
9.5.3	The kidney	175
9.5.4	Intravenous and other injected doses	176
9.5.5	Pharmacodynamics	176
9.6	Weight and obesity	176
9.6.1	General principles	176
9.6.2	Obesity	177
9.7	Sex	178
9.7.1	Absorption and bioavailability	178
9.7.2	Distribution	178
9.7.3	Metabolism	179
9.7.4	Excretion	179
9.7.5	Effects	180
9.8	Pregnancy	180
9.8.1	Physiological and biochemical changes	180
9.8.2	Hormonal effects	181
9.8.3	Transporters	181
9.8.4	The foetus	182
9.9	Ambulation, posture and exercise	182
9.9.1	The gastrointestinal tract	182
9.9.2	Transdermal absorption	183
9.9.3	Tissue distribution	183
9.9.4	Subcutaneous and intramuscular injections	184
9.9.5	The liver	184
9.9.6	The kidneys	184
9.9.7	Body temperature	184
	References and Further reading	185
10	Pharmacogenetics and Pharmacogenomics	187
10.1	Introduction	187
10.1.1	Terminology	187
10.2	Methods for the study of pharmacogenetics	188
10.2.1	Studies in twins	188
10.2.2	Phenotyping and genotyping	188
10.3	<i>N</i> -Acetyltransferase	189
10.3.1	Isoniazid	190
10.3.2	Sulfonamides	190
10.3.3	Other drugs	191
10.4	Plasma cholinesterase	191
10.4.1	Suxamethonium	191
10.5	Cytochrome P450 polymorphisms	192
10.5.1	Cytochrome 2D6	192
10.5.2	Cytochrome 2C9	193

10.5.3	Cytochrome 2C19	194
10.5.4	Cytochromes 3A4/5	194
10.5.5	Other cytochrome P450 polymorphisms	194
10.6	Alcohol dehydrogenase and acetaldehyde dehydrogenase	195
10.7	Thiopurine methyltransferase	195
10.8	Phase 2 enzymes	195
10.8.1	UDP-glucuronosyltransferases	195
10.8.2	Sulfotransferases	196
10.8.3	Glutathione transferases	196
10.9	Transporters	196
10.10	Pharmacodynamic differences	198
	References and Further Reading	198
11	Developmental Pharmacology and Age-related Phenomena	201
11.1	Introduction	201
11.2	Scientific and regulatory environment in regard to younger and older patients	201
11.3	Terminology	202
11.4	Physiological and pharmacokinetic processes	202
11.4.1	Absorption	202
11.4.2	Binding and tissue distribution	203
11.4.3	The blood–brain barrier	203
11.4.4	Liver function	204
11.4.5	Changes in CYP-450 isoforms during the life cycle	204
11.4.6	Renal function	206
11.4.7	Metabolic and pharmacodynamic phenomena	207
11.5	Body surface area versus weight	208
11.6	Age groups	209
11.6.1	Neonates and children	209
11.6.2	Elderly	210
11.7	Further examples	211
	Further reading and references	211
12	Effects of Disease on Drug Disposition	215
12.1	Introduction	215
12.2	Gastrointestinal disorders and drug absorption	216
12.2.1	General considerations	216
12.2.2	Inflammatory conditions of the intestines and coeliac disease	216
12.3	Congestive heart failure	217
12.3.1	Altered intestinal function	218
12.3.2	Altered liver blood flow	218
12.3.3	Altered rate of metabolism – aminopyrine	218
12.3.4	Altered route of metabolism – glyceryl trinitrate	218
12.3.5	Altered clearance – mexilitine	219
12.3.6	Congestive heart failure plus renal problems – toborinone	219
12.3.7	Decompensated and treated CHF – torasemide	219
12.3.8	Oedema	219
12.4	Liver disease	220
12.4.1	Pathophysiology	220
12.4.2	Liver blood flow, binding to plasma proteins, and intrinsic hepatic clearance	220

12.4.3	Methods of investigation	221
12.4.4	Examples	223
12.4.5	Drug effects	225
12.5	Renal impairment	227
12.5.1	General considerations	227
12.5.2	Mathematical approach	228
12.5.3	Examples	229
12.6	Thyroid disease	231
12.6.1	General considerations	231
12.6.2	Examples	231
12.7	Summary	233
	References and further reading	233
13	Quantitative Pharmacological Relationships	237
13.1	Introduction	237
13.2	Concentration–effect relationships (dose–response curves)	237
13.2.1	Antagonism	239
13.2.2	Variation	240
13.2.3	Some illustrations of dose–response curves <i>in vivo</i>	242
13.3	The importance of relating dose–effect and time-action studies	244
13.3.1	The fundamental single dose time-action relationship	245
13.3.2	The fundamental multiple-dose concentration–effect relationship	247
	References and further reading	247
14	Pharmacokinetic/Pharmacodynamic Modelling: Simultaneous Measurement of Concentrations and Effect	249
14.1	Introduction	249
14.2	PK/PD modelling	250
14.2.1	Objectives	250
14.2.2	Single-compartment, time-independent PK/PD models	250
14.2.3	Time-dependent models	251
14.2.3.1	Ebastine and carebastine	252
14.2.3.2	Unequal distribution within plasma: ethanol and glutethimide	252
14.2.4	Hysteresis	254
14.2.5	Pharmacokinetic distribution models	255
14.2.5.1	Thiopental and propofol	255
14.2.6	Receptors in the peripheral compartment models	256
14.2.6.1	LSD	256
14.2.6.2	Digoxin	256
14.2.7	Effect compartment models	258
14.2.8	Warfarin type models	261
14.2.9	Other examples	264
	References and further reading	265
15	Extrapolation from Animals to Human Beings and Translational Science	269
15.1	Introduction	269
15.2	Allometric scaling	270
15.2.1	Refinements to allometric scaling	273

15.2.1.1	Effect of neoteny	273
15.2.1.2	Pharmacokinetic time	273
15.2.2	Practical aspects of allometry	275
15.3	Dose-ranging versus microdosing studies	276
15.4	Statistical approaches	277
15.5	Translational science	277
References and further reading		277
16	Peptides and Other Biological Molecules	279
16.1	Introduction	279
16.2	Chemical principles	279
16.2.1	PEGylation	283
16.3	Assay methods	283
16.4	Pharmacokinetic processes	284
16.4.1	Administration and dosage	284
16.4.2	Bioequivalence	285
16.4.3	Distribution	285
16.4.4	Metabolism	285
16.4.5	Excretion	285
16.5	Plasma kinetics and pharmacodynamics	286
16.6	Examples of particular interest	286
16.6.1	Cholecystokinins	286
16.6.2	Ciclosporin	287
16.6.3	Heparin	287
16.6.4	Trastuzumab	289
16.6.5	Erythropoietin	289
16.6.6	Vasopressin and desmopressin	289
16.7	Conclusion	290
References and further reading		290
17	Drug Interactions	293
17.1	Introduction	293
17.2	Terminology	293
17.3	Time action considerations	294
17.4	Interactions involving drug distribution and metabolism	295
17.4.1	Enzyme induction	295
17.4.2	Enzyme inhibition	295
17.4.3	Plasma protein binding and tissue uptake	295
17.4.4	Mechanisms of enzyme induction	296
17.5	Extent of drug interactions	296
17.6	Key examples	297
17.6.1	Warfarin	297
17.6.2	Cimetidine and ketoconazole	299
17.6.3	Digoxin and quinidine	301
17.6.4	Alcohol and other depressants (notably barbiturates)	302
17.7	Further examples and mechanisms of a wide range of drug interactions	303
17.8	When are drug interactions important?	307
17.9	Desirable drug–drug interactions	307

17.10	Predicting the risk of future drug interactions with new chemical entities	308
17.10.1	<i>In vitro</i> prediction of drug interactions	308
17.10.2	<i>In vivo</i> predictions in human subjects	309
17.10.3	Innovative Phase III clinical trial designs	310
	References and further reading	311
18	Drug Metabolism and Pharmacokinetics in Toxicology	313
18.1	Introduction	313
18.2	Terminology	313
18.3	Dose–response and time–action with special reference to toxicology	314
18.4	Safety studies in new drug discovery	315
18.5	Examples	315
18.5.1	Isoniazid	315
18.5.2	Paracetamol and phenacetin	317
18.5.3	Toxicity associated with prolonged exposure to therapeutic doses	322
18.5.4	Salicylate	323
18.5.5	Toxic chemicals	324
18.5.5.1	Methanol and ethylene glycol	324
18.5.5.2	Halobenzenes	324
18.5.5.3	Miscellaneous	325
	References and further reading	325
19	Drug Monitoring in Therapeutics	329
19.1	Introduction	329
19.2	General considerations	330
19.2.1	Samples and sampling	330
19.2.2	What should be measured?	330
19.2.3	Timing of sample collection	331
19.2.4	Analyses	331
19.2.5	Reference ranges	332
19.3	Specific Examples	332
19.3.1	Antiasthmatic drugs	332
19.3.2	Anticonvulsant drugs	333
19.3.3	Antidepressants	334
19.3.4	Antimicrobial agents	336
19.3.5	Cardioactive drugs	337
19.3.5.1	Digoxin	337
19.3.5.2	Antidysrhythmic drugs	337
19.3.6	Immunosuppressives	339
19.3.7	Lithium	339
19.3.8	Neuroleptics	340
19.3.9	Thyroxine	341
19.4	Dose adjustment	341
19.4.1	Gentamicin	341
19.4.2	Phenytoin	342
19.5	Summary	343
	References and further reading	344

Appendix: Mathematical Concepts and the Trapezoidal Method	345
1 Algebra, variables and equations	345
2 Indices and powers	345
3 Logarithms	347
4 Calculus	347
4.1 Differentiation	347
4.2 Integration	348
4.2.1 Areas under curves	349
4.2.2 Calculating AUC values: the trapezoidal method	349
Acknowledgements	351
Index	353

Preface

The origins of this book can be traced to a previous book with the same title written by one of us (S.H.C.) in 1974, second and third editions being published in 1977 and 1980. At the time, we were both in the early stages of what has become a very enjoyable career-long collaboration. Since that time newer approaches to the subject have been developed and many other books have been published. Mostly these have tended to be either very basic texts on pharmacokinetics, or weightier tomes, although some have been brief introductory texts, while yet others have concentrated on clinical applications. We have aimed to produce a book that takes the middle road, providing sufficient information and background to make it informative, clear, readable and enjoyable, without unnecessary complexity, maintaining the philosophy of the original *Drug Disposition and Pharmacokinetics*. Consequently, this book should be of benefit, in particular, to undergraduate and postgraduate students of science, including pharmacology, toxicology, medicinal chemistry and basic medical science, and students preparing for, and in, pre-professional programmes such as those in pharmacy, medicine and related disciplines, including dentistry and veterinary science, and environmental and public health. However, we are all life-long students, and thus this book is for anyone at any stage in his or her career wishing to learn about drug disposition and pharmacokinetics, that is, what happens to drug molecules in the body, but with strong emphasis on the pharmacological and clinical consequences of drug consumption, and so we expect our book to find readers among researchers, teachers and students in universities, in research institutes, in the professions, in industry, and in public laboratories employing toxicologists and environmental scientists in particular.

Clearly pharmacokinetics cannot be taught without recourse to mathematics. However, understanding the equations in this book requires little more than a basic knowledge of algebra, laws of indices and logarithms and very simple calculus. Anyone wishing to refresh his or her knowledge in these areas is recommended to read the Appendix. In a practical sense, it is important to be able to match standard equations to common graphical displays. There is little need in this context for the ability to derive complex equations. We believe in the old maxim, that a picture is worth a thousand words, and have noted that many of the principal pharmacokinetic relationships can be demonstrated empirically by the movement of dye into and out of volumes of water. We have used this approach to illustrate the validity of several models and further examples and colour plates can be found on the companion web site. This site also contains more mathematical examples, further equations and worked examples for readers who require them.

With few exceptions, we have adopted the system of pharmacokinetic symbols recommended by Aronson and colleagues (*Eur J Clin Pharmacol* 1988; 35: 1) where C represents concentration, A , is used for quantities or amounts, V for volumes of distribution, Q for flow rates, etc. First-order rate constants are either k or, if they are *elimination* rate constants, λ . Numbers have been used to designate compartments rather than letters (letters can lead to confusion, for example between plasma and peripheral) and for the exponents in multiple-compartment models. Thus, the variables for the biphasic decline of a two-compartment model are C_1 , C_2 , λ_1 and λ_2 rather than A , B , α and β , which may be familiar to some readers. It has not been possible to select a single convention for drug nomenclature. Rather, the names most likely to be familiar to readers around the world are used, and so we have leaned towards

recommended International Non-proprietary Names (rINN). In most instances this should not cause problems for the majority of readers: cyclosporin, cyclosporine and ciclosporin clearly refer to the same drug. Where names are significantly different, alternatives are given in parentheses, e.g. pethidine (meperidine), and in the Index.

We have designed this book to be read from beginning to end in the order that we have presented the material. However, there is extensive cross-referral between sections and between chapters – this should aid those readers who prefer to ‘dip in,’ rather than start reading from Page 1. Thus, Chapter 1 is a brief presentation of the general chemical principles underlying the key mechanisms and processes described in the later chapters, effectively a mini-primer in medicinal chemistry. Drug disposition and pharmacokinetics is a discipline within the life sciences that depends entirely on these and other chemical principles. Chapters 2 and 3, which detail distribution and fate of drugs, are largely descriptive. Pharmacokinetic modelling of drug and metabolites, including more advanced concepts of clearance can be found in Chapters 4–7. Chapter 8 is devoted to bioavailability, particularly the influence of tablet formulation on concentrations of drugs in plasma and therefore on clinical outcome. The next four chapters (9–12) deal with what can be referred to as ‘special populations’ or ‘special considerations’: sex, disease, age and genetics in particular. The relationships between pharmacokinetics and pharmacological and clinical effects (PK-PD) are the topic of Chapters 13 and 14, whilst extrapolation from animals to human beings is considered in Chapter 15. The kinetics of macromolecules, including monoclonal antibodies, are considered in Chapter 16. The final chapters exemplify the importance of pharmacokinetics in three clinical areas, considering aspects of drug interactions, toxicity and therapeutic drug monitoring. Thus our sequence is from scientific preparation, through relevant science, to an introduction to clinical applications. The logical extension of the learning process in this area would be obtainable through one or more of the excellent texts available that focus on patient-care orientated pharmacokinetic research and practice.

Our examples come from our own experience, from literature of pivotal significance in the development of the subject, and from drugs that will be especially familiar to readers. Certain drugs stand out as demonstrating basic principles of widespread significance throughout the subject. They include propranolol, warfarin, digoxin, aspirin, theophylline and isoprenaline. It should be noted that these, and several other examples, can be considered as ‘old’ drugs. Some, indeed, such as isoprenaline and guanethidine, are obsolete as therapeutic agents, but still of paramount importance historically and as models. It was with these and other long-established drugs that principles of lasting significance were discovered. Of relevance to this is the fact that interest in this area of science undoubtedly existed among the ancients. More recently, Shakespeare referred to the risk–benefit ratio associated with alcohol consumption in *Macbeth*, and to the duration of action of the fantasy drug consumed by Juliet in *Romeo and Juliet*. Henry Bence Jones was probably the first to describe the rates of transfer of drugs between tissues, in work conducted in the 1860s, after he had developed assays for lithium and quinine. Awareness of the first-order removal of digoxin from the body originates from Gold *et al.* in the 1920s. However, it was in the 1930s that Widmark and Teorell first examined concentrations in blood. In the 1950s and 1960s, Brodie and Williams focused our interest on metabolism and metabolites, and then on quantitative pharmacology related to concentrations in blood. The big explosion of interest resulted from stirrings of pharmacokinetic thought in the colleges of pharmacy, and from the development of Clinical Pharmacology primarily in medical schools, in the 1960s, 1970s, and 1980s. It has been exciting to be associated with this dramatic development in medical science. Mathematical pharmacokinetics first gained prominence in relation to dosage form design, then to profiling of drugs in humans and control of clinical response, and, remarkably, only recently, in the process of new drug discovery.

We have not discussed bioanalysis, apart from a brief consideration of assay specificity in Chapter 19. However, it is important that the reader be aware that pharmacokinetic information can be no better than the quality of the concentration–time data provided. Thus, the pharmacokineticist should ensure that concentration data are from specific, precise and accurate assays, including their application to error-free timing of sample collections. Notes on other methods of drug investigation are to be found throughout the book, and

readers interested in particular methods should be able to access relevant information through the index and references.

We hope that you enjoy this book. We thank our various students in London, Gainesville, Rochester, and too many other locations to mention, for their help in formulating our understanding of our readers' needs in this subject area, and dedicate this book to them. We are immensely grateful to our publishers for their sage advice, and to our families for their support, tolerance and encouragement during the writing of this book.

Stephen H. Curry, Rochester, New York,
Robin Whelpton, London,
January 2010

About the Authors

Stephen Curry

Stephen has been Professor of Pharmacology at The London Hospital Medical College, Professor of Pharmaceutical Science at the University of Florida, and Adjunct Professor of Pharmacology and Physiology at the University of Rochester. He has also spent ten years with AstraZeneca and predecessor companies. He was honoured by the Faculty of Medicine of the University of London with the Doctor of Science Degree and is a Fellow of the Royal Pharmaceutical Society. He currently works in the field of technology transfer and translational science with early stage companies based on discoveries at the University of Rochester (PharmaNova) and Cornell University (ADispell). He can be contacted at www.stephenhcurry.com.

Robin Whelpton

After obtaining his first degree in Applied Chemistry, Robin joined the Department of Pharmacology and Therapeutics, London Hospital Medical College, University of London as research assistant to Professor Curry. Having obtained his PhD in pharmacology, he became lecturer and then senior lecturer before transferring to Queen Mary University of London, teaching pharmacology to preclinical medical students. He is currently a member of the School of Biological & Chemical Sciences and has a wealth of experience teaching drug distribution and pharmacokinetics to undergraduate and postgraduate students of medicine, pharmacology, biomedical sciences, pharmaceutical chemistry and forensic science.

Chemical Introduction: Sources, Classification and Chemical Properties of Drugs

1.1 Introduction

Pharmacology can be divided into two major areas, pharmacodynamics (PD) – the study of what a drug does to the body and pharmacokinetics (PK) – the study of what the body does to the drug. Drug disposition is a collective term used to describe drug absorption, distribution, metabolism and excretion whilst pharmacokinetics is the study of the rates of these processes. By subjecting the observed changes, for example, in plasma concentrations as a function of time, to mathematical equations (models), pharmacokinetic parameters such as elimination half-life ($t_{1/2}$), volume of distribution (V) and plasma clearance (CL) can be derived. Pharmacokinetic modelling is important for the:

- Selection of the right drug for pharmaceutical development
- Evaluation of drug delivery systems
- Design of drug dosage regimens
- Appropriate choice and use of drugs in the clinic.

These points will be expanded in subsequent chapters.

A drug is a substance that is taken, or administered, to produce an effect, usually a desirable one. These effects are assessed as physiological, biochemical or behavioural changes. There are two major groups of chemicals studied and used as drugs. First, there is a group of pharmacologically interesting endogenous substances, for example acetylcholine, histamine and noradrenaline. Second, there are the non-endogenous, or ‘foreign’ chemicals (xenobiotics), which are mostly products of the laboratories of the pharmaceutical industry.

There are numerous ways in which drugs interact with physiological and biochemical process to elicit their responses. Many of these interactions are with macromolecules, frequently proteins and nucleic acids. *Receptors* are transmembrane proteins, with endogenous ligands typified by acetylcholine and noradrenaline (norepinephrine). Although substances may be present naturally in the body, they are considered drugs when they are administered, such as when adrenaline is injected to alleviate anaphylactic shock. Drugs can either mimic (agonists) or inhibit (antagonists) endogenous neurotransmitters. Salbutamol is a selective β_2 -agonist whereas propranolol is a non-selective β -blocker. Some receptors are *ligand-gated ion channels*, for example the cholinergic nicotinic receptor, which is competitively antagonized by (+)-tubocurarine. *Enzymes*, either membrane bound or soluble, can be inhibited – for example neostigmine inhibits acetylcholinesterase

and aspirin inhibits cyclooxygenase. Other proteins that may be affected are *voltage-gated (regulated) ion-channels* – a typical one being voltage-gated sodium channels which are blocked by local anaesthetics such as lidocaine (lignocaine). Antimalarials, chloroquine, for example, intercalate in DNA. Some drugs work because of their physical presence – often affecting pH or osmolarity – for example antacids to reduce gastric acidity or sodium bicarbonate to increase urinary pH and thereby increase salicylate excretion (Section 3.3.1.5).

1.1.1 Source of drugs

Primitive therapeutics relied heavily on a variety of mixtures prepared from botanical and inorganic materials. The botanical materials included some extremely potent plant extracts, with actions for example on the brain, heart and gastrointestinal tract, and also some innocuous potions, which probably had little effect. The inorganic materials were generally alkalis, which did little more than partially neutralize gastric acidity. Potassium carbonate (potash, from wood fires) was chewed with coca leaves to hasten the release of cocaine. Inevitably, the relative importance of these materials has declined, but it should be recognized that about a dozen important drugs are still obtained, as purified chemical constituents, from botanical sources and that alkalis still have a very definite value in certain conditions. Amongst the botanical drugs, are the alkaloids: morphine is still obtained from opium, cocaine is still obtained from coca leaves, and atropine is still obtained from the deadly nightshade (belladonna). Although the pure compounds have been prepared synthetically in the laboratory, the most economical source is still the botanical material. Similarly, glycosides such as digoxin and digitoxin are still obtained from plants. These naturally occurring molecules often form the basis of semisynthetic derivatives – it being more cost-effective than synthesis *de novo*.

Similar considerations apply with some of the drugs of zoological origin. For instance, while the consumption of raw liver (an obviously zoological material) was once of great importance in the treatment of anaemia, modern treatment relies on cyanocobalamin, which occurs in raw liver, and on hydroxycobalamin, a semisynthetic analogue. Another zoological example is insulin, which was obtained from the pancreatic glands of pigs (porcine insulin) but can now be genetically engineered using a laboratory strain of *Escherichia coli* to give human insulin.

Most other naturally occurring drugs, including antibiotics (antimicrobial drugs of biological origin) and vitamins, are generally nowadays of known chemical structure, and although their synthesis in the laboratory is in most cases a chemical possibility, it is often more convenient and economical to extract them from natural sources. For the simpler molecules the converse may be true, for example chloramphenicol, first extracted from the bacterium, *Streptomyces venezuelae*, is totally synthesized in the laboratory. For some antibiotics, penicillins and cephalosporins for example, the basic nucleus is of natural origin, but the modern drugs are semisynthetic modifications of the natural product.

Amongst the naturally occurring drugs are the large relative molecular mass (M_r) molecules, such as peptides, proteins (including enzymes), polysaccharides and antibodies or antibody fragments. Some of these macromolecules, snake venoms and toxins such as botulinum toxin ($M_r \sim 150,000$) have long been known. The anticoagulant, heparin, is a heavily sulfated polysaccharide ($M_r \sim 3,000\text{--}50,000$). Peptide hormones used as drugs include insulin and human growth hormone. Streptokinase, urokinase and tissue plasminogen activator (tPA) are enzymes used as thrombolytic agents. Other therapeutic enzymes are the pancreatic enzymes given to sufferers of cystic fibrosis. Antibodies are a recent addition to macromolecular drugs. Digoxin-specific antibodies, or light-chain fragments (F_{ab}) containing the specific binding site, are used to treat poisoning by cardiac glycosides. Advances in molecular biology have led to the introduction of a number of monoclonal antibodies with a range of targets: various cancers, viruses, bacteria, muscular dystrophy, the cardiovascular and immune systems, to name but some. Furthermore, the antibodies can be

modified to carry toxins, cytokines, enzymes and radioisotopes to their specific targets. Monoclonal antibodies have the suffix *-mab* and the infix indicates the source of the antibody and the intended target; *-u-* indicates human and *-tu(m)-* that the target is a tumour. Thus, trastuzumab is a monoclonal antibody directed at (breast) cancer that has been ‘humanized’, *-zu-*; that is over 95% of the amino acid sequence is human. The prefix is unique to the drug.

With only minor exceptions, drugs are chemicals with known structures. Some of them are simple, some complex. Some of them are purely synthetic; some are obtained from crude natural products and purified before use. Most are organic chemicals, a few are inorganic chemicals. With all drugs, the emphasis is nowadays on a pure active constituent, with carefully controlled properties, rather than on a mysterious concoction of unknown potency and constitution.

1.2 Drug nomenclature and classification

Drug names can lead to confusion. Generally a drug will have at least three names, a full chemical name, a proprietary name, i.e. a trade name registered to a pharmaceutical company, and a non-proprietary name (INN) and/or an approved name. Names that may be encountered include the British Approved Name (BAN), the European Pharmacopoeia (EuP) name, the United States Adopted Name (USAN), the United States Pharmacopoeia (USP) name and the Japanese Approved Name (JAN). The WHO has been introducing a system of recommended INNs (rINN) and it is hoped that this will become the norm for naming drugs, replacing alternative systems. For example, lidocaine is classed as a rINN, USAN and JAN, replacing the name lignocaine that was once a BAN. Often ‘ph’ is replaced by ‘f’, as in cefadroxil, even though the group name is cephalosporins. We have elected to use amphetamine rather than amfetamine. Generally, the alternatives obviously refer to the same drug, such as ciclosporin, cyclosporin and cyclosporine. There are some notable exceptions, pethidine is known as meperidine in the United States and paracetamol as acetaminophen. Even a simple molecule like paracetamol may have several chemical names but the number of proprietary names or products containing paracetamol is even greater, including Panadol, Calpol, Tylenol, Anadin Extra. Spelling can also lead to apparent anomalies. For example, cefadroxine is a cephalosporin (Table 1.2). Therefore it is necessary to use an unequivocal approved name whenever possible.

A rigid system for the classification of drugs will never be devised. Increasingly, it is found that drugs possess actions which would permit their categorization in several groups in any one particular classification system. This is shown most strikingly by the use of lidocaine for both local anaesthetic and cardiac effects. Additionally, with constant changes in drug usage, it is not uncommon to find drugs of several different types in use for the same purpose. The number of examples within each type is of course very large. However, drugs are commonly grouped according to one of two major systems. These are on the basis of action or effect, and on the basis of chemistry. It is not possible to include all drugs in either of these groupings, and so a hybrid classification is necessary if all possibilities are to be considered. Table 1.1 shows an abbreviated pharmacological listing. The interpretation of this is quite straightforward, and it is presented as a general aid to the reader of later chapters of this book. Most of the examples quoted in later chapters are mentioned. Not so straightforward is the chemical listing shown in Table 1.2. It will be immediately noticed that while all of the groups of drugs in Table 1.2 are represented in Table 1.1, all of the types in Table 1.1 are not represented in Table 1.2, as a great many drugs are of chemical types of which there is only a single example, and Table 1.1 is only concerned with those chemical groups of drugs which are commonly known by their chemical names. Commonly encountered chemical groups are exemplified in Table 1.3.

1.3 Properties of molecules

Drug molecules may be converted to other molecules either by spontaneous change (i.e. decomposition) or by enzymatic transformation. Enzymes are such efficient catalysts that the rate of a reaction may be increased

Table 1.1 Abbreviated listing of drug groups categorized on the basis of pharmacological use or clinical effect, with examples, or cross-referenced to the chemical types of Table 1.2

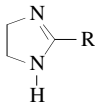
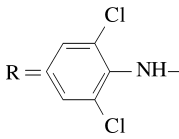
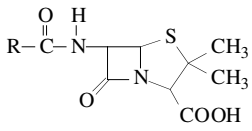
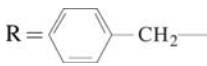
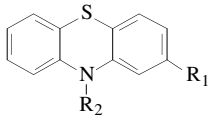
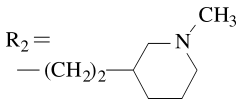
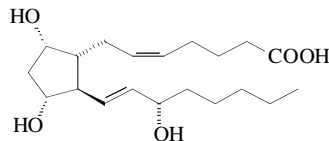
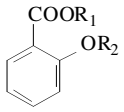
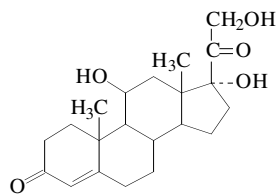
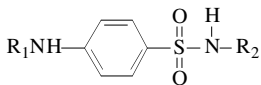
THE CENTRAL NERVOUS SYSTEM	PERIPHERAL SYSTEMS
General anaesthetics	Drugs acting at synapses and nerve endings
I Gases – e.g. nitrous oxide	I Acetylcholine and analogues (parasympathomimetic agents)
II Volatile liquids – e.g. halothane	II Anticholinesterase drugs – e.g. physostigmine
III Intravenous anaesthetics, including some barbiturates	III Inhibitors of acetylcholine at parasympathomimetic nerve endings – e.g. atropine
Hypnotics including some barbiturates and some benzodiazepines, and newer examples such as zolpidem	IV Drugs acting at ganglia – e.g. nicotine
Sedatives including certain barbiturates, phenothiazines and benzodiazepines	V Drugs acting at adrenergic nerve endings, including catecholamines and imidazolines
Tranquillizers	VI Neuromuscular blocking drugs – e.g. suxamethonium
I Major, including certain phenothiazines and butyrophenones	Drugs acting on the respiratory system
II Minor, including certain benzodiazepines	I Bronchodilators – e.g. salbutamol
III Other, newer, examples, such as olanzepine	II Drugs affecting allergic responses – e.g. disodium cromoglycate
Antidepressants	III Oral antiasthmatics e.g. montelukast
I Dibenzazepines – e.g. nortriptyline	Autacoids and their antagonists
II Monoamine oxidase inhibitors – e.g. tranlycypromine	I Histamine and 5-hydroxytryptamine
III Lithium	II Antihistamines – e.g. diphenhydramine
IV Other newer examples, such as fluoxetine	Drugs for the treatment of gastrointestinal acidity
Central nervous system stimulants	e.g. ranitidine and omeprazole
I Amphetamine-related compounds – e.g. methylphenidate and amphetamine	Cardiovascular drugs
II Hallucinogens – e.g. lysergic acid diethylamide	I Digitalis and digoxin
III Xanthines – e.g. caffeine	II Antiarrhythmic drugs – e.g. quinidine
Analgesics	III Antihypertensive drugs, including angiotensin-converting enzyme (ACE) inhibitors (‘prils’)
I Narcotics – e.g. morphine and pethidine	IV Vasodilators – e.g. glyceryl trinitrate
II Mild analgesics, including salicylates	V Anticoagulants, including heparin and coumarins.
Miscellaneous centrally acting drugs, including respiratory stimulants (analeptics), anticonvulsants, certain muscle relaxants, drugs for Parkinson’s disease, antiemetics, emetics and antitussives	VI Diuretics, including thiazidiazines
CHEMOTHERAPY	VII Lipid lowering drugs (e.g. ‘statins’)
Drugs used in the chemotherapy of parasitic diseases, including arsenicals	VIII Thrombolytics (e.g. tissue plasminogen activator)
Drugs used in the chemotherapy of microbial diseases, including penicillins, cephalosporins and sulfonamides	Local anaesthetics – e.g. lidocaine (lignocaine)
Drugs used in the treatment of viral diseases, such as aciclovir	Locally acting drugs
Drugs used in the treatment of fungal diseases, e.g. miconazole	e.g. gastric antacids and cathartics
Drugs used in the treatment of cancer, such as alkylating agents, antimetabolites, anthracycline derivatives, trastuzumab, hormone antagonists	Endocrinology
	Hormones, hormone analogues and hormone antagonists, including steroids, sulfonyleureas and biguanides (e.g. glipizide, thyroxine and insulin)
	Biological response modifiers
	e.g. interferon, adalimumab
	Immunosuppressants
	e.g. ciclosporin

Table 1.2 Some groups of drugs classified on chemical structure rather than pharmacological properties or uses

Group	Parent structure	Chemical example	Uses and examples
Barbiturates		Phenobarbital $R_1 = C_2H_5$ $R_2 = C_6H_5$ $R_3 = H$ $X = O$	As hypnotics and sedatives (pentobarbital) As anticonvulsants (phenobarbital) As general anaesthetics (thiopental)
Benzodiazepines		Lorazepam $R_1 = H$ $R_2 = O$ $R_3 = OH$ $R_7 = Cl$ $R'_2 = Cl$	As anxiolytics (diazepam) As hypnotics (temazepam)
Biguanides		Metformin (as drawn)	As oral hypoglycaemics
Catecholamines		Adrenaline $R_1 = CH_3$ $R_2 = H$ $R_3 = OH$	Sympathomimetic amines
Cephalosporins		Cefadroxil $R_1 =$ $R_2 = CH_3$	As antimicrobial drugs
Coumarins		Warfarin (as drawn)	As anticoagulants
Dibenzazepines		Nortriptyline $R =$ $=CH(CH_2)_2NHCH_3$	As antidepressants
Imidazoles		Miconazole $R = Cl$	As antifungal drugs

(continued)

Table 1.2 (Continued)

Group	Parent structure	Chemical example	Uses and examples
Imidazolines		Clonidine 	As antihypertensive drugs
Macromolecules: Polysaccharides, peptides, proteins, enzymes, antibodies		Heparin, insulin, trastuzumab	In control of blood clotting, diabetes, cancer, rheumatoid arthritis and other conditions
Penicillins		Penicillin G 	As antimicrobial drugs
Phenothiazines		Thioridazine R ₁ = SCH ₃ R ₂ = 	As antihistamines (promethazine) As antipsychotics (thioridazine) As antiemetics (trifluoperazine)
Prostaglandins		PGF _{2z} (as drawn)	As uterine stimulants and other procedures
Salicylates		Aspirin R ₁ = H R ₂ = COCH ₃	As antipyretic, anti-inflammatory and antipyretic drugs
Steroids		Hydrocortisone (as drawn)	Anti-inflammatory drugs
Sulfonamides		Sulfacetamide R ₁ = H R ₂ = COCH ₃	As antimicrobial drugs