DRUGS

DRUGS IN ANAESTHESIA AND INTENSIVE CARE

Edward Scarth | Susan Smith

A new edition of the bestselling essential pocket reference guide for anaesthetists

Features a comprehensive A–Z formulary of all drugs used in anaesthesia and intensive care

Completely revised and updated for the 5th edition

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Drugs in Anaesthesia and Intensive Care

FIFTH EDITION

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Preface to the fifth edition

The aims of this book remain true to those of previous editions. In order to make changes prior to the publication of this edition, a peer review process was undertaken. We have tried to accommodate the changes that were proposed by the reviewers and are grateful for their comments. The book continues in its original structured format, the major changes being the removal of agents no longer in use, the addition of new pharmacological drugs, and the introduction of drug comparison tables and a number of drug structure diagrams. We hope that this new edition will remain popular with critical care professionals, operating department personnel, paramedics, pre-hospital care specialists, and anaesthetists of all grades, in addition to providing sound examination preparation for the FRCA and FFICM. Any comments will be gratefully received via e-mail to edscarth@me.com and susan.smith@glos.nhs.uk.

E.J.S.
S.P.S
Cheltenham, January 2015

Preface to the first edition

The aim of this book is twofold: firstly to summarize concisely the main pharmacodynamic and pharmacokinetic properties of the drugs with which the practising anaesthetist might be expected to be familiar. Secondly, it seeks to introduce the candidate for the FRCAnaes (and, in particular, for the second part of this examination) to an ordered scheme for the presentation of information, which we have found to be of value in both the written and oral sections of the examinations. Examiners are more likely to turn a blind eye to minor errors or omissions of knowledge if they are in the context of a clear and well-ordered presentation. A further advantage of this scheme of presentation is that it allows rapid access to specific information. It is our hope that this compendium will prove to be a useful rapid source of reference for clinical anaesthetists in their day-to-day endeavours, both in the theatre and intensive care unit.

This book is intended to complement, rather than to replace, the standard texts on pharmacology for anaesthetists, since it includes no discussion of the principles of pharmacology, an understanding of which is essential for the clinical use of drugs. We feel that these aspects are very satisfactorily covered elsewhere.

Although our research has been as comprehensive as possible, there will obviously remain some information that will have eluded us, or perhaps remains to be discovered. Many practitioners will disagree with our choice of 172 drugs. Any comments or suggestions will be most gratefully and humbly received in order that further editions of this book may hopefully prove to be more useful.

Finally, we should like to thank the members of the Oxford Regional Drug Information Unit, the many drug company information departments, and all our colleagues for their help and support in this venture. In particular, we should like to thank Professor Roy Spector and Drs John Sear and Tim Peto for their invaluable advice on the manuscript.

M.P.S
S.P.S.
Oxford, 1990

How to use this book

The layout of this book requires some explanation in order for the reader to gain the maximum benefit. The 184 drugs we have included are arranged in alphabetical order to obviate both reference to an index and the artificial categorization of some drugs. Each drug is presented in an identical format and confined to one, two, or three pages under the following headings:

Uses The main clinical uses are listed.

Chemical A brief chemical classification is given.

Presentation The formulations of the commercially available preparations are described.

Main action The fundamental pharmacological properties are briefly indicated.

Mode of action The mode of action at a cellular or molecular level (where known) is described.

Routes of administration/doses The manufacturer's recommended dose ranges are listed in this section; alternative clinical uses are also mentioned.

Effects The pharmacodynamic properties are systematically reviewed. Where a drug has no specific or known action on a particular physiological system, the relevant section has been omitted.

The systems described are:

CVS Cardiovascular system.

RS Respiratory system.

CNS Central nervous system.

AS Alimentary system.

GS Genitourinary system.

Metabolic/other Metabolic, endocrine, and miscellaneous.

Toxicity/side effects The major side effects are listed, with particular reference to the practice of anaesthesia and intensive care.

Kinetics The available pharmacokinetic data are provided. Quantitative data are not available for all drugs, particularly the long established ones. Where information on the absorption, distribution, metabolism, or excretion is unavailable for a particular drug, the relevant section has been omitted.

Absorption Details of the absorption and bioavailability are given.

Distribution This section provides information on the volume of distribution and degree of protein binding of the drug, together with, where appropriate, details of central nervous penetration, transplacental passage, etc.

Metabolism The site and route of metabolic transformation and the nature and activity of metabolites are described.

Excretion The excretory pathways, clearance, and elimination half-life are listed. Although clearances are usually expressed in ml/min/kg, this has not always been possible due to inadequacies in the original source material.

Special points This section describes points of relevance to the practice of anaesthesia and intensive care; in particular, significant drug interactions are reviewed.

This standard format offers great advantages; it enables specific questions to be answered very rapidly. For example, the question 'How is fentanyl metabolized?' may be answered simply by locating the drug alphabetically and then consulting the Metabolism section of the text. This principle holds true for all possible permutations of queries.

Contents

Glossary of terms used in this book

%	percent
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to
±	plus or minus
°C	degree Celsius
®	registered
A2RA	angiotensin II receptor antagonist
ACEI	angiotensin-converting enzyme inhibitor
ACT	activated coagulation time
ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
ADHD	attention-deficit/hyperactivity disorder
ADP	adenosine diphosphate
ALT	alanine transaminase
AMP	adenosine monophosphate
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AS	abdominal system
AST	aspartate transaminase
ATIII	antithrombin III
ATP	adenosine triphosphate
AUC	area under curve
AV	atrioventricular
BRCP	breast cancer resistance protein
Ca^{2+}	calcium ion
cal	calorie
cAMP	cyclic adenosine monophosphate
cf.	confer (compare with)
cGMP	cyclic guanosine monophosphate
cmH_2O	centimetre of water
CNS	central nervous system
CO_2	carbon dioxide
COX	cyclo-oxygenase

CRP	C-reactive protein
CSF	cerebrospinal fluid
CVS	cardiovascular system
CYP	cytochrome
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
ECG	electrocardiogram
EEG	electroencephalogram
e.g.	*exempli gratia* (for example)
EMLA®	Eutectic Mixture of Local Anaesthetics
ESBL	extended-spectrum beta-lactamase
ESR	erythrocyte sedimentation rate
FEV_1	forced expiratory volume in first second
FiO_2	partial pressure of oxygen in inspired air
FVC	forced vital capacity
g	gram
GABA	gamma-amino-butyric acid
GU	genitourinary
HAFOE	high airflow oxygen enrichment
HAS	human albumin solution
HDL	high-density lipoprotein
HepBsAg	hepatitis B surface antigen
HFIP	hexafluoroisopropanol
HIT	heparin-induced thrombocytopenia
HITT	heparin-induced thrombocytopenia and thrombosis
HIV	human immunodeficiency virus
HMGCoA	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
5HT	5-hydroxytryptamine
Hz	hertz
i.e.	*id est* (that is)
IgG	immunoglobulin G
IL-1	interleukin-1
IL-6	interleukin-6
IL-8	interleukin-8
INR	international normalized ratio
ITU	intensive treatment unit
IU	international unit
K^+	potassium ion
kcal	kilocalorie

kg	kilogram
KIU	kallikrein inhibitory unit
kPa	kilopascal
l	litre
LMA	laryngeal mask airway
LMWH	low-molecular-weight heparin
MAC	minimal alveolar concentration
MAOI	monoamine oxidase inhibitor
mb	millibar
MDMA	3,4-methylenedioxymethamphetamine
mEq	milliequivalent
mg	milligram
MIC	minimal alveolar concentration
min	minute
ml	millilitre
mmHg	millimetre of mercury
mmol	millimole
MOP	mu-opioid
mOsm	milliosmole
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRSA	meticillin-resistant *Staphylococcus aureus*
Na^+	sodium ion
NAC	N-acetylcysteine
NAPQI	N-acetyl-p-benzo-quinoneimine
ng	nanogram
nm	nanometre
NMB	neuromuscular-blocking
NMDA	N-methyl-D-aspartate
NO	nitric oxide
N_2O	nitrous oxide
NSAID	non-steroidal anti-inflammatory drug
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
PBP	penicillin-binding protein
PCO_2	partial pressure of carbon dioxide in arterial blood
PEFR	peak expiratory flow rate
PIFE	pentafluoroisopropenyl fluoromethyl ether
PMFE	pentafluoromethoxy isopropyl fluoromethyl ether
PONV	post-operative nausea and vomiting

ppm	part per million
PVR	pulmonary vascular resistance
RDS	respiratory distress syndrome
REM	rapid eye movement
RNA	ribonucleic acid
RS	respiratory system
rtPA	recombinant tissue plasminogen activator
spp.	species
SSRI	selective serotonin reuptake inhibitor
STP	standard temperature and pressure
TCI	target-controlled infusion
TNF	tumour necrosis factor
TPN	total parenteral nutrition
tRNA	transfer ribonucleic acid
UK	United Kingdom
USA	United States of America
V_D	volume of distribution
VD_{SS}	volume of distribution at steady state
VIE	vacuum-insulated evaporator
VMA	vanillylmandelic acid
vpm	volume per million
VRE	vancomycin-resistant *Enterococcus*
vWF	von Willebrand factor
w/v	weight per volume
w/w	weight per weight

Drugs in anaesthesia and intensive care, A–Z

A2RAs

Uses Angiotensin II receptor antagonists (A2RAs) are used in the treatment of:

1. essential and renovascular hypertension
2. diabetic nephropathy
3. congestive cardiac failure, and
4. in patients intolerant of angiotensin-converting enzyme inhibitors (ACEIs).

Chemical A2RAs belong to the tetrazoles group.

Presentation A2RAs are available in tablet, capsule, liquid, and a powder form as an oral suspension. A number of commercially available types are available, including losartan, irbesartan, candesartan, and valsartan. The drug may also be combined with a thiazide diuretic.

Main actions Antihypertensive.

Mode of action A2RAs selectively block the G-protein-coupled angiotensin II receptor AT1, therefore preventing the physiological effects of angiotensin II via the renin–angiotensin–aldosterone system. The drug does not affect bradykinin-induced vasodilatation.

Routes of administration/doses A2RAs are available for oral administration. The specific dose and frequency of an agent administered are dependent on the clinical indication, age of the patient, and particular agent being used.

Effects

CVS A reduction in the systemic vascular resistance occurs, leading to a fall in the systolic and diastolic blood pressures.

GU A2RAs cause a significant increase in the renal blood flow.

Toxicity/side effects A2RAs are generally well tolerated. Dizziness secondary to hypotension may occur. Angio-oedema occurs rarely. The development of a dry cough (cf. ACE inhibitors) is not associated with A2RAs. Hyperkalaemia can occur.

Kinetics Data are incomplete.

Absorption A2RAs are generally well absorbed from the gastrointestinal tract. Bioavailability for some A2RAs are as follows: losartan (33%), irbesartan (60–80%), candesartan (15%), and valsartan (23%).

Distribution The percentage of drug bound to plasma proteins (predominantly albumin) is high: losartan (99.7%), irbesartan (90%), candesartan (>99%), and valsartan (94–97%). The volume of distribution (V_D) of A2RAs is highly variable: losartan (34 l), irbesartan (53–93 l), candesartan (9.1 l), and valsartan (17 l).

Metabolism A2RA metabolism varies widely. Losartan undergoes extensive hepatic metabolism, generating an active metabolite. Irbesartan undergoes hepatic glucuronide conjugation and oxidation to inactive metabolites. Candesartan is a pro-drug presented as candesartan cilexetil, which undergoes rapid ester hydrolysis in the intestinal wall to the active drug candesartan. Valsartan undergoes minimal hepatic metabolism.

Excretion Losartan is excreted 35% in the urine, and 60% in faeces. It has a half-life of 2 hours for the parent drug, and 6–9 hours for its active metabolite. Irbesartan has a half-life of 11–15 hours. Candesartan is excreted 75% unchanged in the urine and faeces, with a half-life of 9 hours. Valsartan is excreted 80% unchanged (83% in faeces and 13% in the urine), with a half-life of 5–9 hours.

ACE inhibitors

Uses ACEIs are used in the treatment of:
1. essential and renovascular hypertension
2. congestive cardiac failure, and
3. diabetic nephropathy.

Chemical ACEIs are derived from peptides originally isolated from the venom of the pit viper *Bothrops jararaca*.

Presentation ACEIs are available in tablet or capsule form, and a number of commercially available types are available, including captopril, enalapril, perindopril, lisinopril, and ramipril.

Main action Antihypertensive.

Mode of action ACEIs inhibit angiotensin-converting enzyme (with an affinity many times greater than that of angiotensin I), so preventing the formation of angiotensin I from angiotensin II. Part of their action may also be exerted through the modulation of sympathetic tone or the kallikrein–kinin–prostaglandin system.

Routes of administration/doses ACEIs are only currently available for oral administration. The specific dose and frequency of an agent administered are dependent on the clinical indication, age of the patient, and particular agent being used.

Effects

CVS The systemic vascular resistance decreases, leading to a decrease in the systolic and diastolic blood pressures; the cardiac output may increase by up to 25%, especially in the presence of cardiac failure.

GU ACEIs cause an increase in the renal blood flow, although the glomerular filtration rate remains unchanged. Natriuresis may ensue, but there is little overall effect on the plasma volume.

Toxicity/side effects ACEIs are generally well tolerated; hypotension, dizziness, fatigue, dry cough (due to an accumulation of bradykinin), gastrointestinal upsets, and rashes may occur. Renal function may deteriorate in patients with renovascular hypertension.

Kinetics Data are incomplete.

Absorption ACEIs are reasonably well absorbed from the gastrointestinal tract. Bioavailability for individual drugs is as follows: captopril (75%), enalapril (40%), perindopril (75%), lisinopril (25%), ramipril (50–60%).

Distribution The percentage of drug bound to plasma proteins is variable: captopril (30%), enalapril (50%), perindopril (76%), ramipril (73%).

Metabolism Captopril undergoes metabolism to a disulfide dimer and cysteine disulfide. Enalapril and perindopril are pro-drugs that are metabolized to their respective active forms. ACEIs undergo minimal metabolism in man.

Excretion ACEIs have markedly variable half-lives and clearance data. The half-life of captopril is 1.9 hours, whereas that of lisinopril is 12 hours, enalapril 35 hours, perindopril 30–120 hours, and ramipril >50 hours. Captopril has a low clearance, compared to enalapril and perindopril which have plasma clearance values of approximately 300 ml/min.

Special points The hypotensive effects of ACEIs are additive with that of anaesthetic agents. However, they do not necessarily protect against the cardiovascular responses to laryngoscopy.

There is an increased risk of renal failure with the co-administration of ACEIs and non-steroidal anti-inflammatory drugs (NSAIDs) in the presence of hypovolaemia.