

Narcotic
Analgesics
in
Anesthesiology

Edited by
Luke M. Kitahata, M.D., Ph.D.
with
J. G. Collins, Ph.D.

Narcotic Analgesics in Anesthesiology

EDITED BY

LUKE M. KITAHATA, M.D., Ph.D.

Professor and Chairman of Anesthesiology
Yale University School of Medicine
New Haven, Connecticut

with

J. G. COLLINS, Ph.D.

Assistant Professor of Anesthesiology and Pharmacology
Yale University School of Medicine
New Haven, Connecticut



WILLIAMS & WILKINS
Baltimore/London



Y072166

Copyright ©, 1982
Williams & Wilkins
428 East Preston Street
Baltimore, MD 21202, U.S.A.

All rights reserved. This book is protected by copyright. No part of this book may be reproduced in any form or by any means, including photocopying, or utilized by any information storage and retrieval system without written permission from the copyright owner.

Made in the United States of America

Library of Congress Cataloging in Publication Data

Main entry under title:

Narcotic analgesics in anesthesiology.

Includes bibliographical references and index.

1. Narcotics--Physiological effect. 2. Analgesics--Physiological effect. 3. Anesthesiology. I. Kitahata, Luke M. II. Collins, J. G. [DNLM: 1. Analgesics, addictive--Pharmacodynamics. 2. Analgesics, addictive--Therapeutic use. QV 89 N222]

RD86.064N37 615'.7822 81-10510
ISBN 0-683-04619-5 AACR2

Composed and printed at the
Waverly Press, Inc.
Mt. Royal and Guilford Aves.
Baltimore, MD 21202, U.S.A.

Narcotic
Analgesics
in
Anesthesiology

Dedicated to my wife

CAROLYN MASSEY KITAHATA, B.A., B.D.

PREFACE

It is the hope of all of those involved in the production of this book that the reader will find in it information that will broaden his or her understanding of the complex actions of the narcotic analgesics. This text was prepared in order to bring together information from many disciplines with the hope that such knowledge would improve clinical use of the opiates as well as promote both development of newer agents and newer techniques of employing older agents.

The authors, in many instances, have made recommendations in this book that are based upon their personal experience as well as on techniques used in other institutions. The editors are indebted to the authors, most of whom are members of The Department of Anesthesiology, Yale University School of Medicine, who took time, in spite of busy work schedules, to contribute to this book. We also thank Ms. Linda Shiffrin and Ms. Gail Norup for the typing of this manuscript. In addition, we wish to thank all of the publishers who granted permission for the use of copyrighted figures in the various chapters of this text.

CONTRIBUTORS

Paul G. Barash, M.D.

Associate Professor of Anesthesiology
Yale University School of Medicine

Glen Z. Brooks, M.D.

Assistant Professor of Anesthesiology and
Obstetrics and Gynecology
Yale University School of Medicine

J. G. Collins, Ph.D.

Assistant Professor of Anesthesiology
and Pharmacology
Yale University School of Medicine

Nicholas M. Greene, M.D.

Professor of Anesthesiology
Yale University School of Medicine

Carl C. Hug, Jr., M.D., Ph.D.

Professor of Anesthesiology and
Associate Professor of Pharmacology
Emory University School of Medicine

Jonathan D. Katz, M.D.

Associate Professor of Anesthesiology
Yale University School of Medicine

Luke M. Kitahata, M.D., Ph.D.

Professor and Chairman of Anesthesiology
Yale University School of Medicine

x CONTRIBUTORS

Charles J. Kopriva, M.D.

Professor of Anesthesiology
Yale University School of Medicine

Carole C. LaMotte, Ph.D.

Assistant Professor of Neurosurgery and
Neuroanatomy
Yale University School of Medicine

Robert H. LaMotte, Ph.D.

Associate Professor of Anesthesiology
and Physiology
Yale University School of Medicine

Yin F. Ngeow, M.D.

Assistant Clinical Professor of Anesthesiology
Yale University School of Medicine

Terence D. Rafferty, M.D.

Associate Professor of Anesthesiology
Yale University School of Medicine

Charles J. Robinson, D.Sc.

Postdoctoral Associate in Anesthesiology
Yale University School of Medicine

Alan F. Ruskis, M.D.

Assistant Professor of Anesthesiology
Yale University School of Medicine

Robert I. Schrier, M.D.

Clinical Professor and Vice Chairman
of Anesthesiology
Yale University School of Medicine

Arthur Taub, M.D., Ph.D.

Clinical Professor of Anesthesiology and
Lecturer of Neurology
Yale University School of Medicine

INTRODUCTION

With the advent of specific narcotic antagonists, narcotic analgesics have been playing a much greater role as primary anesthetic agents. Narcotic analgesics also continue to play an important role in both preanesthetic medication and the relief of postoperative pain. The development of "narcotic anesthesia" has widened the scope of modern anesthetic practice because, when used as the primary agent in clinical anesthesia, narcotic analgesics have the following advantages: minimal cardiac depression, no myocardial sensitization, no known hepatic or renal toxicity, no known teratogenicity, no known occupational hazards, and no evidence of triggering malignant hyperpyrexia.

Historically, the objectives of anesthesia have been four-fold: 1) analgesia; 2) unconsciousness; 3) muscular relaxation; and 4) suppression of untoward reflex phenomena. Among these, analgesia is one of the most important prerequisites for ideal anesthetic agents. The concept of "ether analgesia," originally proposed by John Snow and repopularized by Joseph F. Artusio, shifted the emphasis in anesthesia from the production of unconsciousness to the development of complete amnesia and analgesia and demonstrated that unconsciousness was not an absolute requirement. Clarification of the physiology and pharmacology of neuromuscular transmission and the introduction of various muscle relaxants and their specific antidotes, made the clinical use of such drugs practical and safe. Thus, muscular relaxation is no longer an essential prerequisite for the "ideal" primary anesthetic agent. A better understanding of the autonomic nervous system enabled us to prevent untoward phenomena such as the "vago-vagal reflex." Thus, the most important requirement of an ideal

xviii INTRODUCTION

anesthetic agent is, in addition to its reversibility, the ability to produce analgesia without the side effects of cardiovascular and respiratory depression and acid-base imbalance.

Although narcotic analgesics are known to cause respiratory depression, respiration can easily be controlled during surgical anesthesia, and the availability of the specific antagonist, naloxone, makes the postoperative management of narcotic analgesia easier and safer. However, in addition to respiratory depression, presently available narcotic analgesics have the ability to produce many undesirable side effects (e.g., intraoperative cardiovascular changes, spasmodic episodes of the gastrointestinal tract, postoperative nausea and vomiting, vertigo, withdrawal syndromes). Thus, the search continues for the "ideal" analgesic agent. The clarification of the modes and sites of action of narcotic analgesics is essential for this search.

There have been major developments in the past decade with regard to the clarification of the mechanisms by which narcotics produce analgesia. New developments in neurophysiological techniques have provided insights into the effects of pharmacologically active agents upon specific areas of the central nervous system. Information has been accumulating about specific sites within the central nervous system that are likely to be involved with the modification of pain. Recent developments in receptor binding techniques aided in the discovery of opiate receptors in various areas of the central nervous system. That discovery led to the successful search for endogenous opiates. Thus, the mechanisms and sites of action of endogenous and exogenous opiates are becoming better understood.

This text brings together information from many disciplines in order to increase our understanding of the narcotic analgesics. Chapter 1 details the pharmacokinetic principles that help to clarify our understanding of the complexity of narcotic uptake, distribution, and elimination. Chapters 2 and 3 emphasize the importance of recently discovered information about the sites and mechanisms of action of the narcotic analgesics and the implications of such findings to both clinical and basic science applications. Chapters 4 through 6 present current information about opiate effects on major organ systems. Chapter 7 deals with the use of narcotics in obstetrics. Chapter 8 emphasizes some old and new controversies about the use of narcotic analgesics as premedicants and for postoperative pain control. Chapter 9 presents important concepts for the understanding of narcotic use in drug-addicted patient populations.

Chapter 10 presents some recent concepts in the use of narcotics for the treatment of chronic pain. The final chapter discusses techniques and problems associated with experiments dealing with pain measurements and the determination of narcotic effects upon the sensation of pain.

Throughout this book each author has chosen to use the terminology for the group of drugs, classically known as narcotic analgesics, which he or she feels most appropriate. It is necessary to point out, however, that with the discovery of endogenous opioid substances and with the realization that these drugs have a broad spectrum of action, not associated solely with narcosis, the term narcotic is no longer applicable. In fact, the latest edition of *The Pharmacological Basis of Therapeutics* by Goodman and Gilman states that the justification for the use of the term "narcotic analgesics" is no longer present. The recommendation in that text is that the term opioid be "retained as a generic designation for all exogenous substances that bind specifically to any of several subspecies of opioid receptors and produce some agonistic actions." While the editors recognize the importance of "standard" terminology, they feel that at this point in time the historical importance and strength of both the terms "narcotic analgesics" and "opiates" requires that these terms be retained in the chapters of this book.

CONTENTS

<i>Preface</i>	vii
<i>Contributors</i>	ix
<i>Introduction</i>	xvii
 Chapter 1	
Pharmacokinetics	1
<i>Nicholas M. Greene, M.D.</i>	
<i>Carl C. Hug, Jr., M.D., Ph.D.</i>	
Introduction	1
General Considerations	2
Absorption	6
Distribution	10
Elimination	12
A Pharmacokinetic Model of Mor- phine	12
Significance of Morphine Pharmaco- kinetics	17
Factors that May Affect the Disposi- tion of Morphine	21
Pharmacokinetics of Other Narcotic Analgesics	28
Conclusion	36
 Chapter 2	
Endogenous Opiate Systems and Opiate Receptors	43
<i>Carole C. LaMotte, Ph.D.</i>	
<i>J. G. Collins, Ph.D.</i>	
<i>Charles J. Robinson, D.Sc.</i>	
Introduction	43

xii CONTENTS

	Endogenous Opiates	44
	Locations and Implications of Opiate Receptor Sites	45
	Implications of Multiple Opiate Receptors	51
	Opiate Effects at the Receptor Level	52
	Conclusion	52
Chapter 3	Narcotic Effects on the Nervous System	57
	<i>Luke M. Kitahata, M.D., Ph.D.</i>	
	<i>J. G. Collins, Ph.D.</i>	
	<i>Charles J. Robinson, D.Sc.</i>	
	Introduction	57
	Animal Models of Pain	58
	Possible Sites of Opiate Analgesia ..	60
	Analgesic Synergism	71
	Opiates and Mood	73
	Opiate Effects on Neural Control of Respiration	74
	Opiate Effects on Neural Control of Circulation	77
	Opiate Effects on Cerebral Hemody- namics	80
	Conclusion	82
Chapter 4	Narcotics and the Circulation	91
	<i>Paul G. Barash, M.D.</i>	
	<i>Charles J. Kopriva, M.D.</i>	
	Introduction	91
	Experimental Methodology	91
	Effects on the Central Nervous Sys- tem	92
	Effects on the Heart	95
	Effects on the Peripheral Vascular System	103
	Clinical Application	108
	Narcotic Antagonists	124
	Conclusion	125

Chapter 5	Respiratory Effects of Narcotic Analgesics	133
	<i>Terence D. Rafferty, M.D.</i>	
	Introduction	133
	Premedication	134
	Premedication and Anesthesia	134
	Stiff-Man Syndrome	135
	Postoperative Effects	135
	Peridural and Intrathecal Narcotics	137
	Naloxone Reversal of Narcotic Anesthesia	138
	Conclusion	138
Chapter 6	Effects of Narcotics on the Gastrointestinal Tract, Liver, and Kidneys	143
	<i>Alan F. Ruskis, M.D.</i>	
	Introduction	143
	I. Gastrointestinal Tract	143
	Gastrointestinal Motility	143
	Gastrointestinal Secretions	146
	Effects on Splanchnic Vasculature ..	146
	II. The Liver	147
	III. The Kidney	148
	Conclusion	153
Chapter 7	Narcotics: Mother, Fetus, and Neonate	157
	<i>Glen Z. Brooks, M.D.</i>	
	<i>Yin F. Ngeow, M.D.</i>	
	Introduction	157
	Perinatal Pharmacology of Narcotics	159
	Management of the Neonate	170
	Narcotic Abuse in Pregnancy	171
	Conclusion	172
Chapter 8	Narcotic Analgesics for Preoperative and Postoperative Medication	177
	<i>Robert I. Schrier, M.D.</i>	
	Premedication	177
	Postoperative Medication	182
	Conclusion	184

xiv CONTENTS

Chapter 9	Anesthetic Care of Patients Addicted to Narcotics	189
	<i>Jonathan D. Katz, M.D.</i>	
	Introduction	189
	Complications Resulting From Narcotic Addiction	189
	Preoperative Evaluation	192
	Anesthetic Management	193
	Postoperative Care	195
	Special Considerations	196
	Conclusion	196
 Chapter 10	 Opioid Analgesics in the Treatment of Chronic Intractable Pain of Non-Neoplastic Origin	 199
	<i>Arthur Taub, M.D., Ph.D.</i>	
	Introduction	199
	Assumed Problems of Chronic Opioid Administration	201
	Management of Chronic Opioid Administration	203
	Conclusion	207
 Chapter 11	 Psychophysical Studies of the Effects of Opioid Analgesics on Experimentally Induced Pain	 209
	<i>Robert H. LaMotte, Ph.D.</i>	
	Introduction	209
	Differences in Clinical and Experimental Pain States	209
	Methods of Experimental Pain Production	210
	Psychophysical Measures that could be Obtained in Studies of Experimentally Induced Pain	212
	Effects of Opioid Analgesics on Pain Sensation	215
	Effects of Opioid Analgesics on the Affective Response to Pain Sensation	219

Studies of a Possible Role of Endogenous Opioid Peptides in the Modulation of Experimentally Induced Pain	221
Conclusion	222
Appendix A: Discussion of Sensitivity (d'), Response Criterion and Controversies Associated with their Use	222
Appendix B: Factors to Consider in Designing a Study of the Effects of Opioid Analgesics on Experimentally Induced Pain	224
<i>Index</i>	235

1

Pharmacokinetics

Nicholas M. Greene, M.D.
Carl C. Hug, Jr., M.D., Ph.D.

INTRODUCTION

The use of narcotic analgesics in anesthesia is extensive and involves a wide variety of circumstances. Most are used in analgesic doses to relieve pain or to supplement other anesthetic drugs. Some are used in very high doses as primary anesthetic agents. An understanding of the factors influencing their actions is essential for their safe and effective use. Pharmacokinetics includes those factors affecting the concentration of drug at its site(s) of action, and therefore, the intensity of its effects. This chapter will review the pharmacokinetics of narcotic analgesics.

Pharmacokinetics deals with absorption, distribution, and elimination of drugs. These factors determine the onset, intensity, and duration of drug action.

Many narcotic analgesics are used in clinical anesthesia. Each has advantages and disadvantages. The pharmacokinetics of each differs, but all are governed by the same pharmacokinetic principles.^{29,39,82} These principles can best be discerned by in depth consideration of the pharmacokinetics of a representative narcotic analgesic. To attempt an equally detailed review of the uptake, distribution, and elimination of all narcotic analgesics which can possibly be used in anesthesia would result in such a wealth of data that the pharmacokinetic principles common to all the drugs in this group would be obscured. The following discussion, therefore, emphasizes the pharmacokinetics of morphine, the prototype for narcotic analgesics and still the most widely used drug in this class. We know a great deal about the pharmacokinetics of morphine, and