Narcotic Analgesics in Anesthesiology

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with
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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.

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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

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, spasmotic 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.

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Pharmacokinetics

Nicholas M. Greene, M.D.
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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