Drug Interactions in Anesthesia

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FOREWORD

Modern man accepts drug therapy as a necessary means to attain and maintain good health. If an adverse drug interaction occurs as a consequence of multiple drug therapy, however, modern man does not accept it as an act of God, but rather as a fault for which someone must be held responsible. It is mandatory, therefore, for all anesthesiologists, indeed all physicians, to be fully knowledgeable about drug interactions. That drug interactions do not lead more frequently to problems in everyday living is remarkable, considering the enormous quantity and variety of pills that people ingest. Perhaps interactions are much more common than we appreciate. Patients coming to the operating room are subjected to an intense pharmacologic siege brought about by the drugs introduced by the anesthetist on a body that has already been exposed to other drugs in the preanesthetic period. The possibilities for drug interactions are innumerable. All anesthesiologists must address themselves to and understand this reality.

Anesthesia is the sum of amnesia, analgesia, sedation, hypnosis, relaxation, and attenuation of noxious reflexes.[1,2] As a result of this definition, many anesthetists have concluded that the optimal way to produce the anesthetic state is to use the smallest amount of a variety of drugs, each of which contribute to one of the previously mentioned states. Thus, a common sequence is the frequent use of two or three premedicants before delivery to the operating suite followed by the intravenous administration of atropine or an atropine-like drug. Next comes a small dose of a nondepolarizing muscle relaxant (to minimize fasciculations and muscle pain secondary to succinylcholine), an analgesic, a sedative/hypnotic, the succinylcholine, and then one, two, or three inhalation and/or intravenous agents. The resultant pharmacologic stew produced in the short interval of anesthetic induction is one that our anesthetic ancestors never dreamed about and would probably condemn, being fully aware of the dangers of poly-pharmacy and the difficulty of extricating one drug response from another.

Thus, the anesthesiologist contributes to the phlethora of potential drug interactions now associated with anesthesia and surgery. Is this desirable? Is this something that we should be seeking in the future development of anesthetic agents and adjuvants? I doubt it. Yet the idea of developing a perfect, single-agent anesthetic is not popular at this time, and therefore, anesthetic-induced drug interaction will continue to be a daily reality. For this reason, a text dealing with anesthetic drug interactions is not only relevant but extremely important. The possibility that an understanding of potential drug interactions may allow the more rational development of new anesthetics should not be discounted. The importance of drugs administered hours, perhaps days, after the use of anesthetic agents and adjuvants in the operating or recovery rooms is still another area of concern. There is little doubt that

there will be further anesthetic drug development in the foreseeable future. Hopefully, those who direct or influence our specialty may seriously consider single compounds that can produce the same effects as three others and demand that they be used instead of the multiple-agent approach. Whether this tree will ever bear fruit is difficult to say. It is clear that, for the moment, we must not ignore the complexities of potential and real drug interactions, and that we must try to understand the fundamentals and mechanisms of the subject. Thus, it is important to know and understand the types and mechanisms, as well as the physical and chemical bases, of these interactions. In addition, such seemingly unrelated concepts as competition at the plasma protein level and at receptor binding sites, effects of altered drug excretion, accelerated and/or inhibited drug metabolism, and the importance of physiologic changes and homeostatic alterations to these changes must be fully mastered. It is with a text designed to explore these complex and often difficult-to-comprehend subjects that mastery begins.

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PREFACE

We need not justify the necessity for another edition of a book on drug interactions. Change in this field has occurred at least as rapidly as in other areas of medicine. This swift change is reflected in this second edition by five additional chapters on subjects that either warranted a separate treatment in the first edition or that have matured considerably.

The least change that might be expected during the interval between editions is the detection of new interactions among existing pairs of agents, the combination of suspected interactions, the formulation of new principles, or the application of old principles applied to allow a better understanding of interactions.

All of this has indeed happened, particularly in the application of old principles. During the past several decades, pharmacokinetics has contributed enormously to the intelligent use of the inhaled anesthetic agents. Its contribution to our understanding of the behavior of intravenous agents has until recently been much more modest. Lately, however, pharmacokinetics has contributed increasingly not only to our understanding of individual drugs, but to interactions among them. In fact, it has allowed us to predict specific interactions that have in turn been searched for and uncovered. To recognize the importance of these endeavors, we have added a new chapter on pharmacokinetics, one that complements the information contained in the chapter on mechanisms.

But more exciting information has appeared since the first edition. New drugs and new classes of drugs, as well as new receptor sites and theories, have been investigated and implemented in clinical practice. These new drugs and new classes interact not only with each other, but also with existing agents. The most prominent addition to drugs has been the calcium-channel blockers. This group of drugs has been rapidly introduced into therapy with considerable advantages to the patients but at an increased cost in terms of interactions. We are just beginning to uncover and to explain some of these interactions.

In addition to the chapter on calcium-channel blockers, other headings have been included in the second edition: "Antibronchospastic Drugs," "Antihistaminics," "Antiepileptic Agents," and "Inorganic Cations." This last chapter represents a unique class of drugs, one that has been around since the beginning of medicine, but one that is still poorly understood.

The identification of receptor sites invariably leads to a proliferation of antagonists and agonists/antagonists. Conversely, the development of a pure antagonist agent is essential to help to complete the understanding of the receptor sites and of *endogenous* ligands, that is, the

body's "drugs" that react with the receptor sites. Thus, successively, neuromuscular blocking agents, adrenergic agents, opiates, and benzodiazepines have followed the same pattern of inquiry and development. The benzodiazepine receptor sites are emphasized in a greatly expanded chapter on "Sedatives and Hypnotics," while opiates receive extensive treatment in a carefully crafted revision of "Narcotics and Narcotic Antagonists." Similarly, the chapter entitled "Neuromuscular Blocking Agents" has been revised to reflect the addition of two new agents to the clinical toolbox.

Several other chapters have received careful and extensive revision for the second edition, including chapters 1, 3, 7, 9, 11, 12, 14, 17, 19, 23, 25, 26, and 27. All in all, the second edition contains a considerable amount of new information.

Concerns have been raised about two features in the first edition, one relating to too little information, the other relating to too much. It has been observed that, on the one hand, the emphasis was placed on drugs used in the United States to the apparent exclusion of those used in Europe, for example. On the other hand, it has been perceived that much of the information contained in the first edition was "unnecessary" for practice in the operating room.

In regard to the first point, the contributors must be ultimately selective in the information they present because the number of drugs accessible to the clinician is overwhelming. The contributors to this book have collected information where it is available on drug interactions; frequently, of course, a drug is omitted simply because no interaction information is available. Recently, a phenomenon has occurred that makes a general, comprehensive compendium of drugs difficult to achieve. Many countries have set up their own equivalent to the U.S. Food and Drug Administration. Each of these organizations requires a long, involved process for approval of a new drug. For this reason, few drugs are available in every country; many are available in only a few. Thus, it would be wasteful to try to describe every drug in detail. Fortunately, general principles of drug interactions *usually* apply to classes of drugs, and knowledge of these principles can make possible the prediction of interaction in individual drugs. For example, although individual calcium-channel blocking agents differ in their interactions, major drug interactions should be relatively easy to predict if one is aware of a few guiding principles, as well as the characteristics of each drug of interest.

In regard to the point that the first edition presented information not strictly pertinent to the anesthesiologist, we feel strongly that anesthesiologists must be informed in areas beyond the narrow bounds of the operating room. For example, they must also be aware of drug interactions that occur in the surgical intensive care unit, the medical intensive care unit, the coronary care unit, the emergency room, and the delivery room. The knowledge that ethanol and insulin taken together can lead to profound coma, or of the availability of agents that can quickly reverse benzodiazepine-induced coma, is useful to any anesthetist trained to help in the therapy of comatose patients. In addition, the anesthetist should know not only about the potential interactions among preoperative drugs and anesthetic agents, but also about interactions among those strictly given by the internists because many of these interactions affect the perianesthetic and perisurgical care of the patient. Finally, although the title of the book does refer to anesthesia, the book is also intended as a

reference source for those working outside the field of anesthesia.

The first edition was found clinically useful. In particular, the case-report format has received wide approval. With this encouragement, we have continued this approach in the second edition. We have also adhered to the original chapter arrangement: an initial section on general principles; followed by chapters on the pharmacology and interactions of groups of drugs, chapters complete in themselves, so that the reader will not be forced to peruse several sources for the required information; and a clinical orientation exemplified by abundant case reports.

Finally, we must extend our thanks to Robin A. Brien, Administrative Assistant to Dr. Smith, for her invaluable help in coordinating the editorial phases of this publication.

We hope that you enjoy reading this book, and that we may hear from you concerning its usefulness, whatever your area of interest.

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DANGERS AND OPPORTUNITIES

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The first known anesthetic death could have been prevented by knowledge in a specific area of drug interactions. Mortality and morbidity continue to arise from our understandable ignorance of many facets of this subject. On the other hand, drug interactions have helped to transform the course of anesthetic management, which currently relies on the skilled administration of several drugs to the same patient. Certainly, combination therapy and drug interactions are the basis of "balanced" anesthesia. Hence the art lies in the avoidance of hazardous interactions and in the expert application of useful ones. This introductory chapter examines the role of drug interactions in the practice of anesthesia. The emphasis is on the practical side of the subject, including the contributions of research to the clinical understanding of drug interactions.

CASE REPORT

In 1848, 16-year-old Hannah Greener came under the care of Dr. Meggison, a country practitioner near Newcastle, England, for the removal of a great toenail. She was terrified of the impending procedure, and accepted gratefully the offer of the new anesthetic agent, chloroform. This only partially calmed her, and she approached the operation with fear. The story of her sudden death during the first few whiffs of chloroform and of the futile attempts to resuscitate her with brandy is too well known to repeat here. There is now little doubt that her death was a direct result of the interaction between chloroform and the excess epinephrine discharged from her adrenals. Had Dr. Meggison chosen ether, her life probably would have been spared. The clarification of the cause of Hannah's mysterious death had to wait over half a century for the classic studies of Goodman Levy, who demonstrated unequivocally that chloroform sensitizes the myocardium to the dysrhythmic actions of epinephrine.[1,2]

Even today, physicians often wait until an interaction has occurred and then ascertain the cause, rather than anticipate an interaction on theoretical grounds. The major difference is that, because of an expanded pool of pharmacologic knowledge, the time scale of this sequence has been compressed—from over 60 years in the case of chloroform, to a few hours or days.

A Useful Drug Interaction

Drug interactions have exerted a profound effect on the development of modern anesthesia. Neuromuscular blocking agents are an example. Previously, adequate muscle relaxation could be obtained only with the primary anesthetic agent, usually ether. This relaxation was achieved at the risk of profound central nervous, circulatory, and occasionally respiratory depression. The introduction of muscle relaxants allowed the use of lower concentrations of potent inhaled agents, or even their abandonment in favor of the intravenous agents. The latter led to the implementation of the concept of "balanced" anesthesia, which meant balancing the dosage of drugs with different actions to

provide adequate amnesia, muscle relaxation, analgesia, and attenuation of reflexes.

The safe use of curare was certainly an essential feature of this revolution in anesthetic practice. The changes brought about by curare, however, were not the consequence of the introduction of a single drug, but were due to the skillful exploitation of the interactions among three drugs: curare, neostigmine, and atropine. It is not an overstatement to claim that the rapid expansion of modern surgery is closely connected with the purposeful application of drug interactions.

Dangers and Opportunities

The guiding principles, then, of the succeeding chapters are avoiding or at least attenuating undesirable and dangerous drug interactions, using desirable and useful interactions to maximum advantage, and converting ostensibly undesirable interactions into useful ones.

One example should suffice for the last principle. About 25 years ago, the combination of ether and curare was banned in our training program because of a well-known study by Beecher and Todd,[3] who had demonstrated that the mortality following the combination was 1 in 50. Thus my teacher's suggestion to use ether and curare for a case met with my resistance. He explained that the basis of the ether-curare combination was marked synergism, and the solution was simply to use less of each drug, particularly curare. Today we should take this principle for granted—when there is synergism or addition between two agents, less of one, or preferably of both, should be used. However, one still sees, for example, nondepolarizing blocking agents administered on a fixed schedule, irrespective of the anesthetic used. The result can be troublesome, particularly with halothane, enflurane, or isoflurane. Small increments of the neuromuscular blocking agent and low concentrations of the inhaled agent will suffice, with adjustment of muscle relaxation according to the concentration of the inhaled agent. This approach takes advantage of a drug interaction, rather than being controlled or hindered by it.

The "Ideal" Opiate Antagonist

The evolution of opiate anesthesia and the opiate antagonists illustrates a useful drug interaction, as well as the search for the "ideal" drug interaction. Ideally, an antagonist should (1) have no effect of its own, (2) reverse only the "undesirable" effects of the agonist, and (3) last longer than the agonist. The first is easily attained. The third, a long duration of action, is nebulous, since the opiates vary considerably in this respect. If the antagonist administered in the recovery room lasts too long, pain relief may be delayed. The second criterion (selective antagonism) is even less well defined. The definition of desirability depends upon the circumstances. For example, the amphetamines have hypertensive, anorectic, and cortical stimulating properties. Each of these properties may be desirable if the agent is used to elevate blood pressure, decrease the appetite, or elevate the mood; the other two automatically become side-effects. The opiates, with their protean effects, are no exception. Physicians often employ the usually undesirable effect of ventilatory depression in patients who are resisting the ventilator, and the somnolence produced by some opiates is considered desirable in patients on long-term ventilation. It is currently an open question whether specificity of action should be built into the agonists themselves, or into the antagonists.

An Interaction Gone Astray

Occasionally, a useful drug combination goes beyond its original intent. The addition of epinephrine to a local anesthetic is an example. Its usefulness in decreasing the toxicity and prolonging the duration of the local anesthetic is well documented. In the presence, however, of certain inhaled

agents, particularly halothane, an additional and undesirable interaction may occur: a decrease in the dysrhythmic threshold to epinephrine. We now know that enflurane and isoflurane are better agents to use in the presence of exogenously administered epinephrine, halothane permits limited use, and cyclopropane is unacceptable. Interestingly enough, the presence of lidocaine increases the threshold to epinephrine-induced dysrhythmias.[8]

Still another unanticipated interaction is the advance warning that epinephrine may provide against local anesthetic toxicity. If rapid intravascular absorption following injection of the test dose occurs, it may be difficult to detect any effects of the anesthetic, whereas those of epinephrine are usually obvious—tachycardia, palpitations, and headache. If these manifestations are present, one should assume that significant amounts of the local anesthetic have also been absorbed and that central nervous system toxicity may occur on further injection.

On the other hand, if the epinephrine is absorbed slowly during a peridural anesthetic, as is appropriate, still another type of interaction occurs. Blood pressure and systemic vascular resistance may actually *decrease* more when epinephrine is in the anesthetic solution than when it is not.[4] Why should this happen when the original drug interaction depended on the vasoconstrictive properties of epinephrine? In high concentrations, as present in the epidural space, epinephrine does have an *alpha*-adrenergic (vasoconstrictive) action. In low concentrations—diluted in the bloodstream—it acts as a *beta*-adrenergic substance. Presumably this vasodilating action adds to the vasodepressant effects of lidocaine—both direct and indirect from the sympathetic block—to produce noticeably greater hypotension. Thus a drug interaction that began as straightforward has become complex.

RESEARCH INTO DRUG INTERACTIONS

The rest of this chapter will deal with the state of research into drug interactions, and with the impact of this research on daily practice. Research is defined here as any concerted effort that increases our knowledge and allows the useful transfer of that knowledge to the practicing physician.

The Problem of Definitions

The terminology used to describe drug interactions is in a sad state. The lack of standard definitions has created a problem in this book, since we must use terms as other authors have used them, and their definitions either vary or are nonexistent. For accuracy, I shall outline below some of the definitions that have been proposed. For the sake of standardization, I shall give my own preferences.

The commonly used terms are *addition*, *antagonism*, *synergism*, and *potentiation*. Before synergism or antagonism can be defined, there must be some agreement on the definition of *addition*, or the mode of summation of drug effects. Two definitions of addition are generally used: (1) *dose addition*, when one-half the dose of drug A plus one-half an equi-effective dose of drug B evokes the same effect as the entire dose of drug A or drug B alone; (2) *effect addition*, when the intensity of the combined effect equals the sum of the intensities of the effect that each drug evokes when administered alone. Effect addition is certainly additive behavior as it may be expected from a superficial examination; each drug simply brings its own effect into the partnership. I prefer the dose-addition definition, although with dose-addition, the combined drug effect is not so obvious. It is more easily understood by considering a simple experiment. Equipotent amounts of drug A and drug B can be established. If upon administration of one-half of each of these amounts, the same effect is achieved as from either drug alone in its

full amount, dose addition exists. The same is true if we use one-third of drug A and two-thirds of drug B, one-quarter of drug A and three-quarters of drug B, one-fifth of drug A and four-fifths of drug B, etc. Thus the one moiety of the combined drug does not add its own effect to that of the other moiety, but complements the effect of the latter exactly to the intensity that would be achieved by the sum of the fractional doses if both were fractions of either A or B.

Synergism has been defined as a type of interaction in which the effect of a combination of drugs is greater than the effect of (1) any drug given singly, (2) the combined effects of the drugs, or (3) the effect of the sum of the drugs, i.e., greater than addition as defined in the previous paragraph. The third definition might be called *dose synergism*, and in keeping with our acceptance of the dose addition concept, I prefer this definition.

The first definition of synergism is the one most widely used or implied in case and clinical reports. The rationale given is that synergism literally means "working together," and any combination that gives a greater effect than either drug alone is synergistic. However, it would seem that if the effect of the combination of two drugs is less than the sum of the effects of the drugs, the drugs are actually working against each other. For example, if two lumberjacks can saw down trees at the rate of ten trees each per day, and if together they can saw down only 12 trees, it would seem that somehow they were working against each other, perhaps by getting in each other's way; the relationship is in fact antagonism.

Potentiation has had several definitions, most of them the same as the definitions given for synergism above. I prefer the following definition: the enhancement of action of one drug by a second drug that has no detectable action of its own. Thus, although cocaine has no sympathomimetic action of its own, it potentiates the action of epinephrine.

In its simplest form, the definition of *antagonism* is the opposing action of one drug toward another. When drugs exert opposite physiologic actions, as do nitroprusside and methoxamine, or when an inactive drug diminishes the effect of an active drug (naloxone and a narcotic) the understanding of the concept of antagonism, physiologic or pharmacologic, is straightforward. However, when two drugs produce a similar effect, they may still antagonize each other if the combined effect is less than that of the sum of the drugs, as defined by dose addition.

We can thus summarize the aforementioned definitions: additive interaction may be represented by $2 + 2 = 4$; synergism by $2 + 2 = 5$; potentiation by $0 + 2 = 3$; and antagonism by $0 + 2 < 2$; $1 + 2 < 3$; or $2 + 2 < 4$.

The Present State of Drug Interaction Research

Quantifying Drug Interactions. The quantification of drug interactions is an interesting part of pharmacology in which one goes beyond the stage of saying that, for example, synergism is present, and tries to determine how much. This area, however, is replete with complex notions, large numbers of curves placed together on the same graph, and difficult mathematic calculations. Research is usually done *in vitro*, or in animals, at best. It is therefore beyond the scope of this book. Suffice it to say that research into the quantification of drug interaction is still in a rudimentary state, and is rarely useful to the clinician.

The extent of knowledge of interactions among more than two drugs is even more discouraging. Few studies even semiquantitatively examine the interaction among three agents, and none has attempted more than three. The experiments are long, the data involve four dimensions, and the display of data requires a three-dimen-