Drug Interactions in Anesthesia

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Lea & Febiger • 1981 • Philadelphia

Library of Congress Cataloging in Publication Data

Smith, Norman Ty, 1932–
Drug interactions in anesthesia.

Includes index.
1. Drug interactions. 2. Anesthesiology.
I. Miller, Ronald D., 1939– joint author.
II. Corbascio, Aldo N., joint author. III. Title.
[DNLM: 1. Drug interactions. 2. Anesthesia.
3. Anesthetics. QV38 S655d]
RD82.7.D78S6 615'.781 80-17454
ISBN 0-8121-0683-0

Published in Great Britain by Henry Kimpton Publishers, London

PRINTED IN THE UNITED STATES OF AMERICA

Print No. 4 3 2 1

"To Penelope, Marilyn, and Elise:

The beacons which light our way."

Preface

The practice of anesthesia entails a daring incursion into human pharmacology and pharmacodynamics. The anesthesiologist performs daily a complex experiment in patients, with drugs that profoundly affect essential functions, such as respiratory, cardiovascular, and neuromuscular activity. To achieve anesthesia speedily and effectively often requires many agents (six to ten on the average) in patients who may have been exposed to 20 or even more drugs in the preoperative period. There are few other branches of medicine in which polypharmacy is such a necessity and drug interactions such an inevitable consequence. However, the impressive growth of available drugs witnessed during the past two decades has been troubled by the realization that the pharmacodynamics and pharmacokinetics of one drug may be seriously modified by the presence of other drugs. This leads to numerous interactions, some welcome, some less so. The science of interactions is still in its infancy, but it constitutes an area of explosive development that is bound to affect many traditional therapeutic concepts.

At present, the anesthesiologist faces the problem of drug interactions without any useful guide that is both detailed and clinically oriented. The aim of this book is to provide such guidance and to introduce some logic and method into one of the most persistent problems of anesthetic practice. The book explores at least four facets of the interaction process: mechanism, detection,

prevention, and management. The approach is mainly clinical and practical. Thus when confronted with a patient who is receiving diuretics and antihypertensives, for example, the anesthesiologist will be able to refer to a systematized approach, rather than to isolated fragments of pharmacologic knowledge. Although we have stressed the clinically important drug interactions, we do discuss those that are less clinically relevant, but that have been overemphasized elsewhere.

We divided the book into two sections. The first five chapters cover some general principles dealing with drug interactions. This section is particularly useful in understanding the subsequent chapters, which describe specific groups of drugs and their interactions. These initial chapters will help to develop an insight into the mechanisms of drug interactions, and to prepare the reader for the inevitable situation involving a new interaction—real or imagined.

The subsequent chapters are arranged according to classes of drugs. The contributors were asked to follow a plan in the writing of a chapter. To emphasize the clinical orientation of the book, each chapter was to include one or more case reports describing a drug interaction, followed by detailed pharmacology of that particular group, especially the pharmacology pertinent to drug interactions. Then the chapter was to bring together case report(s), pharmacology, and advice to the physician on the management of a patient receiving one or more drugs from that class of agents.

The authors did, by and large, succeed in these deceptively modest requests. Inevitably, the order and manner of presentation have varied among the chapters. How successful our somewhat different approach is, and which chapter arrangement offers the best teaching, must be decided by the reader. Any comments will be welcome.

We decided to divide the clinical chapters according to groups of drugs to provide a handy reference for the evening before an operation, for example. Thus for the patient receiving antihypertensive and diuretic therapy, the two appropriate chapters can be read to determine the potential problems arising from these drugs during anesthesia. Similarly, the choice of an anesthetic agent or the wisdom of a choice already made can often be appraised by consulting a single chapter.

The format of this book should thus please those who use it as a reference. Those who read it straight through as a text will find some overlap, which is intentional. We did not wish to force the reader to peruse several chapters to discover all the information required about a single agent.

The number of possible drug interactions seems almost limitless. We have restricted ourselves to those that occur during anesthesia and operations, or those that may otherwise be important to the anesthesiologist. The latter group takes into account the anesthesiologist's role in areas outside the operating room, such as in the intensive care unit. Since there have been so many false alarms concerning drug interactions, we have defined, when possible, the incidence and clinical relevance of an interaction. This has not always been easy. Many interactions have been described only with anecdotes. Others have been observed only in animals.

Although this book was designed for the practicing or in-training anesthetist, there is enough general information on drug interactions to satisfy many others: the medical student, the pharmacologist, and the internist, to name but a few.

The carefully chosen authors have been given considerable latitude, even to the point of disagreeing with each other. In drug interaction, as in other medical fields, there are no absolutes, and the state of knowledge is such that disagreement and change are inevitable.

It is routine to thank one's editor. However, special thanks are due to Mr. George Mundorff, who has surely been one of the most patient editors, even through the elephantine conceptional period of this

book. We wish to thank our authors, who have been willing to try a different format of presentation. Our gratitude ultimately goes to the many investigators who have pioneered in this complex but vital subject. We hope that others will follow in this critical area of knowledge and trust that this book will provide a guide and an incentive.

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Contents

Chapter 1

Dangers and Opportunities

N. TY SMITH

The first recorded anesthetic death could have been prevented by a knowledge of drug interactions. Mortality and morbidity still continue from our understandable ignorance of the 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 adrenal medullae. 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, we in medicine often wait until an interaction has occurred and then determine 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 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 inhalation 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 hypnosis, 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. Some 20 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, pancuronium administered on a fixed schedule, irrespective of the anesthetic used. The result can be troublesome, particularly with enflurane. Small increments of pancuronium and low concentrations of the inhalation agent will suffice, with adjustment of muscle relaxation according to the concentration of the inhalation agent. This approach takes advantage of a drug interaction, rather than being controlled or hindered by it.

The "ideal" narcotic

The evolution of narcotic "anesthesia" and the narcotic 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 narcotics 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. (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 narcotics, with their protean effects, are no exception. We often use the usually undesirable effect of ventilatory depression in patients who are resisting the ventilator, and the somnolence produced by some narcotics is considered desirable in patients on long-term ventilation. I believe that specificity of action should be built into the agonists themselves, rather than 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 anesthetic is well documented. In the presence, however, of certain inhalation agents, such as halothane, an additional and undesirable interaction may occur: a decrease in the arrhythmic threshold to epinephrine. We now know that enflurane and isoflurane are the optimal agents to use in the presence of exogenously administered epinephrine, halothane permits limited use, and cyclopropane is unacceptable.

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 manifestations of the anesthetic, whereas those of epinephrine are usually obvious—tachycardia, palpitations, and headache. If these symptoms are present, one should assume that significant amounts of the local anesthetic have also been absorbed and that CNS (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 blood stream—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.

Definitions

The terminology used to describe drug interactions is in a sad state. That the definitions of the terms are not standard 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 the sake of completeness, 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 one-half of each of these amounts is then administered and the same effect is achieved as from either drug alone in its full amount, then dose addition exists. The same will hold 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. Thus the one moiety of the combined drug does not add its own effects 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 dose addition, I prefer this definition.

The first definition seems to be the most popular 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.

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 use of the word 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 quantitation 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 purview of this book. Suffice it to say that research into the quantitation 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 discouraging. Few studies even semiquantitatively examine the interaction among three agents, and none has attempted more than three. The experiments are very long, and the display of data requires a three-dimensional plot. That the simplest technique requires one dimension for each drug[5] has discouraged most investigators.

Even the qualitative description of multiple-drug interactions can be overwhelming. Thus we were unable to find an author willing to write a chapter on this subject. The problem must be faced, however; the large number of drugs used by anesthesiologists and other physicians mandates it. It is not unusual for the anesthetist to use six to ten drugs per patient, including preanesthetic medication. Preoperatively, a patient may receive more than 40 medications concurrently, many of which are multicomponent preparations![6]

This information on multiple-drug interaction is important. One would intuitively expect that the interaction among quinidine, a nondepolarizing neuromuscular blocking agent, and an antibiotic would be more severe than that between any two of these agents.

The incidence of drug interactions. Still another difficulty in drug-interaction research has been in estimating the incidence of drug interactions in hospitalized patients in general and not just in those particular patients undergoing anesthesia and surgical procedures. Some attempts have been made,[6,10] but the results vary considerably. Problems arise from variations in the strictness of criteria for the incidence and the clinical relevance of a drug interaction, from whether a study was prospective or retrospective, from the attitude of physicians toward filling out "yet another form," and from whether an interaction or just a potential interaction was reported. (A potential interaction means that two or more drugs that *might* cause an interaction are administered to the same patient.)

One attempt to estimate the incidence of drug interactions has been to establish the relationship between the number of drug *reactions* and the total number of drugs given. It is assumed that this relationship should be linear; that is, twice as many drugs should produce twice the incidence of reactions. Thus any greater increase in drug reactions would be partly due to drug interactions. According to Table 1–1, the number of drug reactions does increase out of proportion to the increase in the number of drugs consumed. One could argue, however, that a larger number of drugs taken indicates a more severely ill patient, and that reactions are determined partly by the condition of the patient.

Bringing information to the physician. Of more interest to the practicing physician than the methodology and the rigidity of assessing drug interactions is the accumulation and maintenance of an accurate mass of information about well documented drug interactions, and a method for disseminating this information in a clinically useful way. This is even more difficult than it sounds. The widespread circulation of inaccurate, poorly documented, or clinically irrelevant information has retarded the general acceptance of the medical significance of drug interac-

Table 1–1

Number of Drugs Given	Reaction Rate (%)
0–5	4.2
6–10	7.4
11–15	24.2
16–20	40.0
21+	45.0

(From Smith, J. W., Seidl, L. G., and Cluff, L. E.: Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility. Ann. Intern. Med., 65:629, 1966.)

tions. Although certain examples of enhancement of toxicity or antagonism of beneficial effects resulting from the use of specific drug combinations are widely recognized by physicians, in general the substantial number of potential drug interactions and the pharmacologic complexities involved in many of these interactions have made it impractical for most anesthesiologists to have adequate drug-interaction information available when therapy is prescribed, when the patient is evaluated, or when anesthesia is administered.

There are a few reliable sources of information on drug interactions. None of them emphasizes the interactions of interest to the anesthesiologist, although some do provide information for those wishing to explore the problem further. Hansten has written a book that summarizes a large number of interactions in a convenient and easy-to-read format.[11] The American Pharmaceutical and Medical Associations have sponsored a book that goes into more detail.[12] It includes short treatises on groups of drugs and the interactions within these groups, as well as a number of succinct monographs dealing with individual drug-drug interactions. The National Institutes of Health have published three enormous volumes, which cover all of the drug interactions reported or investigated between 1967 and 1974.[13] These volumes are a valuable resource for the serious student of drug interactions, but they are impossible to carry around on preanesthetic rounds. In contrast to these large books is a small drug interaction "wheel" (Medisc, Excerpta Medica Services). Whereas this pocket-sized device is probably of more interest to internists, and whereas it gives no other information than the possibility of an interaction, it does alert the physician as to when to seek more information.

It would not be surprising, however, if the physician were wary of schemes that claim to specify drug interactions, since the history of drug interaction recounts many false alarms. In the case of the antihypertensive agents, we have successively believed that reserpine, guanethidine, *alpha*-methyldopa, and propranolol are all dangerous drugs to the anesthetized patient, and that they should be discontinued before operation if at all possible. We have repeatedly conveyed this information to our colleagues. It is no wonder if they do not believe us any more. Many patients were denied timely operation because of this belief. The attitude toward various antihypertensive agents has changed several times over the past few years: (1) We now believe that many of the initially reported problems were due not to the drugs but to the disease and the resulting propensity to labile arterial pressures. (2) Current opinion suggests that to withdraw some antihypertensive agents (clonidine or propranolol) can be dangerous or even lethal. (3) Perhaps therapy *should be initiated before anesthesia* in patients with uncontrolled hypertension. (4) Finally some have gone so far as to suggest that a *beta*-adrenergic blocking agent should be given prophylactically before induction of anesthesia in any patient in whom it is desirable to avoid hypertensive episodes.

Another consideration in transmitting drug-interaction information properly to the physician is the classification of drug interactions in a way that can provide guidelines for dealing with the interaction effectively. Although drug interactions are often thought of in absolute terms, they represent only one of many factors influencing the clinical response to drugs. Moreover, most interacting drug combinations *can* be given concurrently if the interacting potential is kept in mind by the physician and proper adjustments in dosage or route of administration are made, as demonstrated in the case of ether and curare.

The Stanford MEDIPHOR system and the report class-designation developed by Cohen et al.[6] provides in a convenient manner both necessary information and useful guidelines. A brief description of this report class-designation follows. In general, Class 1 contains interactions having clinically sig-