Comparative Evaluation of New Inhalation Anesthetics

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A NEED for a new anesthetic is evidenced by the lack of a completely satisfactory anesthetic. Many older agents are flammable, and several of the newer nonflammable agents produce toxicity.[1-5] By "toxicity" we mean untoward effects which persist after the drug has been eliminated from the body or appear at some later time following its use. (This ignores the classic definition, which includes a dose-time-related, pan-species, predictable pathologic change induced by a drug. The classic definition would not allow us to call halothane a hepatotoxin or methoxyflurane a nephrotoxin.) In addititon to toxicity, several currently accepted agents have undesirable pharmacologic properties, such as depression of vital functions or production of arrhythmias.

The search for a new anesthetic is hampered by the limited guidelines defining the tests and order of evaluation of a new agent. Furthermore, there are limited guides as to which results warrant acceptance or rejection of a new anesthetic or further study. Finally, there is no example of a progressive, in-depth study of a new anesthetic which incorporates what we believe are important features of such an evaluation: comparisons with accepted drugs; imposition of stress to evaluate toxicity of the agent under adverse conditions; measurement of metabolism and influence of metabolism on toxicity; studies in volunteers. In this essay we present a comprehensive method of evaluating a new anesthetic (fig. 1). This methtod has been influenced in part by our experiences in the evaluation of two new inhaled anesthetics, enflurane (Ethrane ‡) and Forane.‡

The development of a new anesthetic proceeds through four stages of assessment, each successive stage contingent upon favorable results in the preceding stage. These stages are: the initial synthesis, preparation and evaluation by the manufacturer; studies of toxicity in aimals; evaluation of pharmacologic and toxic effects in volunteers; and finally, general evaluation through widespread clinical usage.

Chemical Synthesis and Initial Animal Screen

The essential features of any new inhalation anesthetic are non-flammability, chemical stability, and relatively low solubility. The advantages of nonflammability are obvious. It is readily achieved by halogenation [6, 7] of the molecule, but halogenation also decreases the vapor pressure. A reasonably low (100 to 300 torr) vapor pressure is desirable because it makes the compound a liquid at room temperature, which improves ease and cost of handling. However, a vapor pressure which is too low invites high solubility, as with methoxyflurane and trichloroethylene. In any event, the solubility of the agent, particularly in blood, must be determined. The finding of high solubility would diminish enthusiasm for the agent, since such a property prolongs induction of and recovery from anesthesia. Fluorination may enhance molecular stability, but excessive fluorination decreases potency.[8, 9] Chlorination and bromination, while increasing potency, may produce compounds which are more readily attacked by ultraviolet light, alkali, or hepatic enzymes.[10]

Thus, an acceptable compound is a nonflammable liquid stable in the presence of ultraviolet light and alkali. Having produced a compound circumscribed by these requirements, the manufacturer determines whether that compound produces anesthesia in mice without producing obvious untoward effects, such as convulsions, pulmonary edema, or death. If the findings are favorable, a similar evaluation is made in dogs. In addition, proclivity for production of arrhythmias, either spontaneous or in response to epinephrine ad-

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ministration, is tested. Excessive arrhythmogenicity might cause the compound to be discarded at this or a later stage (fig. 1). (A more detailed consideration of evaluation of a new drug by a manufacturer is provided by Dr. Abrams in another part of this symposium).

Broad Animal Screen

Once a new inhalation agent has been shown to be anesthetic and not to have apparent toxic or adverse effects, more detailed studies of toxicity are initiated, either by the manufacturer or by independent investigators, or both. It has become apparent in recent years that regardless of who the investigators are, a more systematic and detailed evaluation is needed. This evaluation must include not only determination of absolute toxicity but also a comparison of the effects of the new agent with those of anesthetics in current use. A new agent may have adverse effects, but to progress beyond study in animals these must be no more adverse than those associated with accepted anesthetics. This comparative aspect requires some standard of equipotency. It is meaningless to compare effects at dissimilar doses when toxicity itself may be dose-dependent. We have chosen MAC, the minimum alveolar concentration necessary to prevent movement in response to incision of the skin in 50 percent of animals, as our gauge of dose.[11] Ideally, comparisons should be made at several multiples of MAC. However, this is rarely done because of the inordinate expenditure of effort and money necessary.

The significance of animal studies may be limited by the lack of an animal which mimics man in all his parts. Although no one animal perfectly imitates man, we hope to imitate him organ by organ by testing for toxicity in several species. We might choose specific organs in specific animals where these organs are similar in structure or function to the same organ in man. For instance, we might test for neuromuscular function in cats or liver function in pigs. Testing in several species is also more likely to uncover a species uniquely sensitive to a particular toxic effect, such as the miniature swine,[12, 13] which develops malignant hyperthermia when anesthetized with halothane or chloroform. The FDA has recognized the need for such broad testing, and requires use of at least four species in evaluation of toxicity of new anesthetics.[14] Selection of species is guided by our desire to imitate man but limited by the availability, cost, and ease of handling of particular animals. These characteristics limit the use of the most attractive of animals, the monkey. A primate should be included in the detailed animal studies. However, the dog and cat are frequently selected because they are readily available and reasonably easy to handle, and because a large pool of comparative data has been obtained with these animals. Of course, if such data are not applicable to man they are of little value regardless of their quantity. Small animals such as mice and rats fulfill the requirements of availability, low cost, and ease of handling. They make possible the use of large numbers, which is statistically advantageous. However, the strains used are so inbred they may respond uniquely to the anesthetics.

Simple, uncomplicated anesthesia may fail to elicit toxic effects. Evaluation of the effects of an anesthetic in the presence of stress of one form or another is indispensable to any study of toxicity. The types of stress that might be studied are legion. Stresses common to clinical practice include prolonged anesthesia, with or without hypoxia, hypercapnia, or hypotension. Have studies during stress provoked a previously unsuspected toxicity? Prolonged, repeated anesthesia revealed lethal neurotoxicity of one new agent, Baxter 2986, and thereby precluded further studies.[15] Hypoxia and hypercapnia enhanced the hepatic injury from chloroform anesthesia.[16] Starvation may have a similar effect in animals ex-

FIG. 1 (facing page). The order of development of new inhalation anesthetics depicted as stages which lead eventually to marketing of the compound. The major reason for discarding a drug, once a chemically acceptable one is synthesized, is toxicity, as shown on the left side of the figure. As the agent's physical and pharmacologic properties are elucidated and compared with those of currently-used anesthetics, increase or loss of enthusiasm for the new agent occurs, as shown on the right side of the figure. Few agents reach the marketing stage.

posed to methoxyflurane or chloroform.[17] Hypocapnia increases the convulsive propensity of enflurane.[18, 19] Other stresses which may be considered—but have not been applied to new aesthetics—include hypovolemia, anemia, and hyperthermia. Tests which stress organ function, tests which evaluate complex enzymatic activities of tissues, and studies of metabolism of a drug all may be helpful in detecting organ toxicity. Function tests which elicit a maximum organ response are more likely to uncover toxicity. For instance, a dose of bromsulphalein which taxes the excretory capacity of the liver may uncover a small decrease in hepatic reserve.[20] Similarly, sensitive enzymatic tests such as the serum glutamic pyruvic transaminase test in search for liver abnormalities are more likely to uncover subtle injury. Information about metabolism of a new anesthetic may give a clue to its toxicity. However, it is both difficult and costly to identify all metabolites and determine the relative toxicity of each both in animals and in man. It would be of great advantage to have an agent which is not metabolized. Lack of metabolism would be suggested by a lack of difference between the concentrations of the agent in the blood entering and leaving the organ where biotransformation occurs, usually the liver. Using this approach, Halsey [21] found no extraction of Forane or cyclopropane by the liver of the miniature swine. Metabolism would have been suggested by the appearance of a difference across the liver. Sawyer [22] has demonstrated such differences for halothane and fluroxene. Moreover, he has shown increases in the fractions extracted by the liver as anesthetic partial pressure is lowered. This may relate immediately to the report by Leong [23] that prolonged exposure (245 hours) to subanesthetic concentrations (1/10 MAC) of methoxyflurane or halothane produces toxic effects in rats, guinea pigs, and rabbits. We suggest that these toxic effects may have resulted from the production of far larger absolute amounts of metabolites than would be produced by a deeper but more brief anesthetic exposure, although the time–dose products might be equal for the anesthetic and subanesthetic exposures. For example, administration of five hours of 1.25 to 1.5 MAC halothane every other day or every third day for a total of four exposures to dogs and monkeys produced no evidence of hepatic damage,[24, 25] although these experiments are comparable to Leong's experiments in terms of the time–dose product (that is, 245 hours × 0.1 MAC vs. 20 hours × 1.5 MAC). In contrast, in Leong's experiment the animals exposed to halothane and methoxyflurane had slower weight gains, increased liver–body weight ratios, and altered hepatic architecture when compared with unexposed controls. Exposure to diethyl ether gave no evidence of toxicity. This represents the only demonstration of halothane hepatotoxicity in animals of which we are aware. Such studies of the effects of prolonged administration of subanesthetic concentrations constitute an exciting new approach to the evaluation of anesthetic toxicity from noxious metabolites. Parenthetically, it is worth noting that such exposure approximates that which an anesthetist might receive.

Many drugs are used concomitantly with anesthetics, both for anesthesia and for other purposes. Any evaluation of a new anesthetic must include an appraisal of the interaction of these drugs with the anesthetic. Such concomitant administrations also may be viewed as stresses. Of concern are the interactions of anesthesia with two classes of drugs: those that patients are apt to receive prior to anesthesia and those used in the course of anesthesia. The former group might include digitalis, antihypertensives, hormones, hallucinogens, and central nervous system stimulants such as amphetamines and tranquilizers. The latter group might include narcotics, nitrous oxide, belladonna compounds and vasopressors. A drug interaction often tested in animals is that of anesthesia and epinphrine.[26] Large differences exist among anesthetics. Six times as much epinephrine is needed to produce arrhythmias during fluroxene anesthesia as during equivalent doses of halothane anesthesia.[27] Forane is similar to fluroxene, giving it a clear advantage over halothane in this area. It is difficult to predict the anesthetic–epinephrine–arrhythmia relationship: an isomer of Forane, enflurane, apparently produces sensitivity similar to that produced by halothane.[28]

The teratogenicity of the agent must be tested before the new anesthetic is used in women of child-bearing potential or in very young patients. Current FDA guidelines suggest studies in four animal species with search for effects on estrus, impregnability, the fertilized ovum and implantation, organogenesis and morphology, late fetal development, parturition and postnatal development. The effects of both acute and chronic repeated exposures must be tested. Such experiments must be comparative, since all anesthetics studied have some teratogenetic effects.[29-32] The real question is, does a new agent show a greater tendency to produce such effects?

Studies in Man

The overriding purpose of animal studies is the definition of the toxic effects of the new agent. During the initial studies in animals, only an incidental search is made for pharmacologic effects, both because of the greater importance of toxicity and because pharmacologic effects in animals may have only qualitative relevance to man. Although initial studies in man still have evaluation of toxicity as a primary purpose, at this level of evaluation we are also interested in defining the pharmacologic effects of the new inhalation anesthetic (fig. 1).

In the past there has been no uniform sequence of human testing of new anesthetics. The first exposure of man to fluroxene was a brief anesthesia of the investigator, followed promptly (the same day) by use in a surgical patient by that investigator.[33] Halothane[34] and Forane[35] were used first in patients. Enflurane was used first in human volunteers.[36] Initial use in patients offers the advantage of evaluation of the agent in the milieu in which it will be used. Further, the onus of unexpected toxicity may be less if some benefit is derived from the surgery–anesthesia incident (*i.e.*, surgical correction). On the other hand, it may be difficult to discriminate toxic effects induced by anesthesia from those contributed by other factors. These might include the disease necessitating the operation, premedication, or intraoperative adjuvants such as muscle relaxants, surgical stimulation, and blood loss. Clearly, testing should not be done first in the desperately ill or terminal patient who has "little to lose." In such circumstances it may be impossible to separate anesthetic toxicity from deterioration due to disease.

We seek to uncover harmful effects before they produce irreversible injury. To do this, we impose progressive increases in stress in terms of both anesthetic dose and duration and gradual superimposition of ancillary stresses such as surgery, disease, and old age. Since the approach must be comparative, we must also have a standard of anesthetic dose and data on the effects of commonly-used anesthetics. We cannot predict what injuries may be produced. This ignorance necessitates a "shotgun" approach, which not only involves multiple tests of a single organ function but, more importantly, tests of function of multiple organs. These may include tests of effects on not only the liver and kidney, but also muscle, fat, intestine, hematopoiesis, clotting, blood electrolytes, and endocrines. Nonspecific evidence of cellular injury, such as serum glutamic oxalacetic transaminase and serum or urinary lysozyme, may also be sought. There is an endless list of studies which might be performed. The only limits are imposed by economy, the expertise and imagination of the investigators, and the well-being of the subjects.

Brief Volunteer Exposures

For the initial studies in man we propose a limited stress. Healthy, young volunteers would be exposed to 15–60 minutes of subanesthetic concentrations (one fourth MAC). Anesthetic dose may be predicted from the dog MAC and from the oil/gas partition coefficient.[37] In this and subsequent studies, search is made for adverse effects on hepatic and renal function. Incidental to these studies is the measurement of anesthetic uptake and elimination.

Next, the stress would be increased by increasing the anesthetic dose. Another group of healthy young volunteers would be exposed to a brief period of anesthesia of sufficient depth to permit endotracheal intubation. Effects on arterial and right atrial pressures, electrocardiogram, electroencephalogram, and temperature would be measured. In this group, arterial and venous blood gases, cardiac

output, and alveolar anesthetic concentrations would be measured. This experience would provide the investigators with the character of the anesthetic state, including the pattern of induction, degree of jaw or muscle relaxation, tendency for reflex irritability, pattern of emergence, and postanesthetic morbidity, such as nausea.

Prolonged Volunteer Exposures

Presuming these two studies provide confidence in the safety of the new agent and give some hint of its efficacy, we would proceed to more detailed and stressful studies. The first of these would impose prolonged exposure to the agent in oxygen at constant, normal Pa_{CO_2}. We would initially avoid the stress of elevated Pa_{CO_2} because of the suggested tendency of hypocapnia to impair hepatic function.[38] Toxicity remains a primary concern. As before, kidney and liver functions would be tested. We would also examine the effects on the brain, both through use of the electroencephalogram and through testing of mental function. Interest in the electroencephalographic and cerebral metabolic effects of anesthetics has been heightened by the occasional convulsive effects of one new anesthetic, enflurane.[18] Enflurane induces a dose-related increase in EEG-wave frequency, terminating in a multiple-spike pattern and grand mal seizures.[39, 40] The EEG seizures are sometimes reflected in muscle twitches or tonic–clonic movements. As noted earlier, these findings may be induced or accentuated by hypocapnia. Do the convulsive patterns reflect a serious detrimental effect? No measurable neurologic sequelae have resulted in either animals or man.[41, 42] Although oxygen consumption increases during seizures, there is no evidence of cerebral hypoxia: cerebral arterial–venous oxygen differences for the brain are no greater than awake values.[42] It has even been suggested that the appearance of twitches might be interpreted as a useful sign of excessive depth or ventilation.[36] Mental function testing in which comparisons of postanesthesia with preanesthesia status are made requires an enormous effort, but provides the best current measure we have of any subtle toxic central effect. James [44] has provided evidence of detrimental postanesthesia changes in mood and intellectual function. Similarly, Davison has found such effects for halothane and Forane.[45] However, halothane and Forane differ in the severity of changes elicited, halothane producing greater and more prolonged dysfunction. Although no permanent effects have been seen with either agent, one of the aims of testing was to uncover any sustained damage.

While the primary goal of examining toxicity is pursued, we may also study the pharmacologic properties of the agent. This provides maximum economy of use of the volunteers. The requirement of constant Pa_{CO_2} precludes studies of respiration, and our efforts in these first experiments have concentrated on the anesthetic dose-related circulatory responses to the new agent. Studies of circulation are of particular importance since we are often unable to compensate for untoward effects. Such effects might cause us to discard an anesthetic which possessed otherwise desirable properties. We are interested in deviation from the norm (awake state) and direct harm, as evidenced by arrhythmias, impairment of myocardial reserve, or inadequate perfusion. The measurement of arrhythmias is as easy as the assessment of the other two is difficult. We have used some relatively uncommon but noninvasive methods such as determination of the I-J wave amplitude of the ballistocardiogram [46] and heart-cycle intervals (time-corrected preejection period [47]) for studying myocardial reserve. Indices of circulatory adequacy include the ratio of cardiac output to oxygen consumption and the development of metabolic acidosis. Our studies have failed to demonstrate inadequacy of perfusion for the common anesthetics [48–51] or for Forane [52] by these techniques. Whether they would reveal a subtle noxious effect remains in question. Changes in circulation from the norm may occur with many anesthetics. One must be cautious in interpreting particular deviations as "good" or "bad." For example, is the dose-related decrease in arterial pressure with Forane good or bad? While perfusion pressures of vital organs such as brain, heart and kidney are reduced and may result in injury, particularly if the organs are already compromised by arteriosclerosis or pre-existing paren-

chymal disease, the workload of the heart is also reduced, thereby decreasing myocardial oxygen demand. An evaluation of deviation from the norm cannot be made in isolation, but must be considered in light of the entire pattern of circulatory response.

Other ancillary studies include analyses of neuromuscular effects and anesthetic metabolism. Neuromuscular studies might demonstrate an impairment of neuromuscular transmission, particularly by fatigue in response to high-frequency tetanic stimulation. Such a study has revealed a significant difference between Forane and halothane,[53] a difference which was later reflected in Forane's potentiation of the neuromuscular blockade produced by *d*-tubocurarine.

The FDA requires studies of metabolism as part of the toxicologic evaluation of any new drug. Although of considerable theoretical value, a study of metabolic products appears to be of limited practical value. Toxicity should be revealed by specific studies of toxicity. Isolation of the metabolites of a new drug is difficult and requires knowledge of the pathways of metabolism. Assigning toxicity to the metabolites may be equally difficult, particularly since we cannot estimate the concentration of metabolic product at the site of biotransformation. The concentration at that site, or at any concentrating site such as the kidney, may be far higher than that in the blood, urine, or expired gas, where measurements are usually made. Because of the difficulty of measuring metabolites, some investigators have chosen to measure the amount of anesthetic which can be recovered following anesthesia.[54, 55] If most of the drug could be recovered, this would suggest that if any toxic products were formed, they must be in low concentration. It would be a clear plus for a new anesthetic if the findings compared favorably with accepted anesthetics.

Presuming the previous studies have demonstrated safety and favorable pharmacologic properties, we would increase the stresses applied in volunteers. This also would be an inevitable result of the evaluation of certain properties of the anesthetic. Studies would be performed during spontaneous ventilation with concomitant elevations of Pa_{CO_2}. The tests used previously would be applied to determine the alterations produced by elevated Pa_{CO_2} in cardiovascular, toxicologic and central nervous system effects of the anesthetic. Not only might toxicity be enhanced by elevation of Pa_{CO_2}, but such elevation might induce arrhythmias. These studies also offer the opportunity to evaluate the effects of the anesthetic on respiratory rate and volumes, Pa_{CO_2}, and ventilatory and circulatory responses to imposed increases in Pa_{CO_2}. The last three are of particular importance. Pa_{CO_2} defines the extent of respiratory depression. The responses to imposed increases of CO_2 provide an estimate of the reserve of the body to meet respiratory or cardiovascular stresses. Elevations of CO_2 normally cause an increase in sympathetic outflow which produces cardiovascular stimulation. Anesthetics impair this combined response; the extent to which they impair it may determine the extent to which they impair the responses to stresses such as hypoxia and hypovolemia. Halothane diminishes this response as much as any anesthetic,[56] whereas the ethers[57, 58] appear to affect it least. It would be desirable that a new anesthetic not obtund this response more than halothane.

Most potent inhaled anesthetics are used in combination with nitrous oxide, and the effect of this combination should form part of the evaluation of the agent in volunteers. Nitrous oxide produces a weak alpha-adrenergic stimulation, leading to vasoconstriction, increased peripheral resistance and increased arterial pressure.[59, 60] Thus, prolonged anesthesia with nitrous oxide, is a stress to the sympathetic nervous system. The use of nitrous oxide also necessitates a reduction of Pa_{O_2} and dissolved oxygen and, hence, may reduce the transport of oxygen to tissue. This may be of particular importance in the presence of vasoconstriction induced by nitrous oxide.

Limited Clinical Trials

Studies in patients may begin after demonstration of sufficient evidence of safety of the agent relative to current anesthetics in volunteers. At a minimum, we believe this includes tests at constant normal Pa_{CO_2} and at elevated Pa_{CO_2}. Some would argue that before a new

anesthetic is used in patients it must be shown that it has distinct advantages over available agents. Others believe a new compound need only offer an alternative to currently available agents.

Studies in patients present a number of opportunities that studies in volunteers do not. Potency, that is, MAC, for man may be determined. Although MAC can be estimated from volunteer studies, precise determination requires a surgical incision. Second, although prospective studies in a small number of volunteers are likely to reveal major or predictable toxicity, use of the anesthetic in large numbers of patients in a common clinical setting is necessary to rule out more subtle or relatively rare (*i.e.*, sensitization) toxic effects. Finally, patient studies offer the opportunity to study a multiplicity of new and clinically important stresses and drug interactions.

Studies in patients offer the severest test of a new agent's innocuousness. The patient provides stresses not found in volunteers. These include a wide range of ages, presence of limited cardiorespiratory or organ function, the stimulus of surgery itself, and use of other drugs prior to and during anesthesia. The organ with limited reserve, for instance the kidney in a diabetic patient, may respond far differently from that of a healthy volunteer. In a healthy young volunteer the autonomic nervous system may antagonize the direct cardiovascular depressant effects of an anesthetic. This favorable response may be attenuated in the aged, where profound cardiovascular depression may replace the healthy balance obtained in the young.

The principles which guide our selection of volunteers also would guide our selection of patients. The initial studies would be made in healthy young patients without concomitant administration of ancillary drugs or superimposition of severe surgical stress. As confidence is gained, we would extend studies to include older, more debilitated patients. Any study in the elderly presupposes an estimate of the change in anesthetic potency produced by aging. Although such has been determined for halothane,[61] it is not known whether those results are applicable to other anesthetics. Testing in the elderly must precede wide clinical use.

Some stresses may provide benefit to the patient. Surgical stimulation may reverse cardiovascular or respiratory depression. We have measured such reversals for halothane and Forane, and the effect seems to be greater with Forane.[62] For example, the blood pressure increases incident to surgery are two to three times as great with Forane as with halothane when each is used at a dose equalling 1.25 MAC.

Patients who receive anesthesia commonly receive a multitude of other drugs as well. It is important to know the compatibility of the other drugs with the new agent. The combination of the anesthetic with premedicant drugs such as narcotics, barbiturates, belladonnas and tranquilizers should be investigated. Some premedicants reduce anesthetic requirement.[63] This (*i.e.*, MAC change) can be tested. Premedication may alter the response to the anesthetic in other less desirable ways. For example, Jones [64] found that morphine changed the positive cardiac output response to cyclopropane to a negative one. The effects of narcotics on respiration are well known. One might be leery of combining an anesthetic which is a potent respiratory depressant with morphine before that interaction has been measured.

Both the anesthetist and the surgeon administer drugs during anesthesia. The anesthetist frequently administers ultrashort-acting barbiturates, muscle relaxants, belladonnas, and/or vasopressers, and less frequently gives cardiotonics such as digitalis. One example of a hazardous combination was suggested by Eger [65]: administration of succinylcholine during induction with halothane or cyclopropane in two young, healthy, unmedicated volunteers was followed by several minutes of multifocal ventricular extrasystoles. No arrhythmias occurred in seven subjects given succinycholine during induction with fluroxene. In this regard it would be clearly advantageous for a new agent to resemble fluroxene more than halothane or cyclopropane. The surgeon commonly injects epinephrine or instills antibiotics. The advantages and hazards of the interactions of these medicines with anesthetics are well known, but deviations provided by a new anesthetic must be tested. The interactions of anesthesia with epinephrine and

TABLE 1. Compounds Recently Tested for Anesthetic Properties

Name and/or reference number	Formula	Studied in		Reason for Discarding
		Animals	Man	
Reference[70]	$CHF_2CF_2CH_2Cl$	Yes	Yes	Arrhythmias
Halopropane[71, 72, 73]	$CHF_2CF_2CH_2Br$	Yes	Yes	Arrhythmias
Teflurane[74,75,76]	CF_3CHFBr	Yes	Yes	Arrhythmias
Ohio TCMF[77, 78]	$CCl_3CF_2OCH_3$	Yes	Yes	Hypotension; mucous membrane irritation
Baxter 29S6[15, 79]	CF_2CHCF_3 O CH_2Cl	Yes	No	Neurotoxicity

with muscle relaxants are of particular interest. The favorable interaction of Forane and epinephrine in dogs (no sensitization of the myocardium) relative to that of halothane must be tested in man. The method devised by Katz and Matteo [66] could be used with the addition of a larger range of doses of epinephrine.

Interactions of the anesthetic and other drugs may be desirable, as opposed to the previous examples of unwanted effects. Miller *et al.*[52] have recently found that Forane compared with halothane potentiates the effects of *d*-tubocurarine. This is advantageous because reversal of relaxation should be more readily accomplished following the smaller dose of *d*-tubocurarine administered during Forane anesthesia. It also implies that the elimination of Forane itself may be sufficient to reverse the paralysis. Miller's studies also have underscored the importance of anesthetic dose in the interaction of the anesthetic with a neuromuscular blocking agent: the effect is dependent on the anesthetic dose as well as the dose of the neuromuscular blocker.[67] This fact has important implications for the testing of anesthetic–relaxant interactions of both new and old anesthetics, and underscores the importance of comparability of anesthetic doses.

BROAD CLINICAL TRIALS

A broad survey of patient responses to a new anesthetic represents the last step in the evaluation of anesthetic toxicity before the drug is marketed. What prior studies have not established are subtle, unexpected or rare (*e.g.*, sensitization) toxicity, differences in responsiveness or general patient acceptance. Such items as rapidity of awakening, duration of care in the recovery room, occurrence of nausea, return of appetite and oral intake, temperature and weight changes, length of hospitalization, and mortality, could be determined. Such a survey might be expanded along the lines of a drug surveillance program to include analyses of the interactions of new and common anesthetics with preanesthetic administration of drugs (hormones, antihypertensives, stimulants, hallucinogens, diuretics—the list is as long as the pharmacopeia), genetic characteristics (race, blood type, handedness, or even eye color) and disease (reader fill in). The value of such a program has been demonstrated by the results obtained in the Boston study.[68] A further aid in the identification of unwanted effects might be the limitation of the new agent's use to three or four widely-separated geographical areas. It may be that toxic effects of an anesthetic are not manifest for several months following anesthesia. Such morbidity or mortality would not be apparent in a hospital-based study but would appear as a public-health statistic. The limitation of the agent to several areas where stable populations exist, therefore, would make possible the suspicion or identification of such an untoward effect.

The Problem Remaining

Even the possession of information from all the above studies does not always make the decision to accept or reject a new anesthetic a simple one. There are a few instances where no problem exists and, in fact, several potential anesthetics have been discarded because of obvious toxicity (table 1). On the surface, toxic effects are simple to evaluate in that all are undesirable. But, how does one

balance an adverse effect with one agent (*e.g.*, hepatic necrosis) against a different effect of another (*e.g.*, EEG seizure activity). A decision becomes still more difficult when one considers differences in magnitude and incidence. Would you prefer a 1:10,000 chance of hepatic failure or a 1:10 chance of "harmless" convulsion? Worse yet are the decisions to be made on the basis of pharmacologic effects. The price paid for obtundation of airway reflexes may be respiratory depression. As noted above, reductions in cardiac output and arterial pressure may compromise an organ whose perfusion is marginally adequate, but at the same time the reduction in myocardial work might be a benefit to the heart. All of this suggests that the perfect anesthetic may be unobtainable. Our choices may be between shades of gray rather than black or white. The decisions may be difficult or even impossible, but choose we must, for fall is coming with its harvest of new anesthetics.[69]

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