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Halothane—A New Perspective

There are no harmless substances; there are only harmless ways of using substances—EMIL MRAK, *Member, Commission of Pesticides*

ANY CHRONIC EXPOSURE of a biologic system to a foreign chemical will produce changes in that system depending on 1) the duration of exposure and 2) the concentration achieved as a result of that exposure. The changes range from organ malfunction or failure to teratogenic, mutagenic and carcinogenic effects.

The volatile anesthetics have come under extremely close scrutiny in recent years to determine why adverse reactions resulting in organ malfunction occur occasionally in patients. These studies have progressed to a point that the possible mechanisms of this type of acute toxicity can now be envisioned. However, new questions are being raised concerning the possible effects of long-term exposure to low levels of these agents, such as operating room personnel may experience. From the studies of organ toxicity it has become clear that metabolism of the anesthetic is required for toxicity, although other factors are important also. For example, halothane normally is metabolized to nontoxic metabolites though, at least in rats, hepatic necrosis results when the exposure occurs under low oxygen tensions using animals pretreated to maximize the drug-metabolizing activity.* It has become obvious in the presence of low oxygen tensions the pathway of metabolism of halothane is altered, resulting in the formation of toxic intermediates. The mechanism of hepatic toxicity apparently involves the covalent binding of the metabolites produced in this altered pathway. Most important, however, is the fact that a combination of conditions must be precisely met in order for the toxicity to develop.

Studies of possible mutagenicity and carcinogenicity secondary to chronic exposure to anesthetics have not advanced to the extent of the acute organ toxicity studies. Chronic studies are difficult and expensive to conduct because they are extremely time-consuming. This area of research has also been confused by a few inadequately planned experiments resulting in studies that were poorly controlled or in which only extremely high concentrations of anesthetics were examined. This latter point is of extreme importance, since when enough anesthetic is used any number of effects are possible. In an area of research as important and as emotionally charged as this, only careful studies should be reported and emphasized; therefore, the timely study of the effects of halothane on fertility, reproduction, and postnatal survival by Wharton *et al.*,[1] reported in this issue, is most welcome. This study was carefully planned to yield a threshold level at which some toxicity related to fertility and reproduction develops. These investigators exposed mice daily for nine weeks prior to mating and also continued the exposure of the females through pregnancy. The levels of exposure were 0.025, 0.1, 0.4, 1.2, and 4.0 MAC hours per day. It is startling to find that the major effect was on the overall pregnancy rate, but only at the two highest concentrations. There was an effect on the weight of mothers at 0.4 MAC hour, but this level of exposure had no effect on reproduction. Most important, the results indicate that there is a considerable margin of safety between the lowest exposure at which an effect was seen and the concentration found in the operating room. When the 0.4 MAC hour exposure is taken as the lowest dose at which an effect was seen, as the authors point out, this is 40 times the expected exposure in an unscavenged room, and an order of magnitude or more greater when the room is scavenged.

It is refreshing to find that there may be a considerable margin of safety in the long-term exposure to halothane and possibly other volatile anesthetics, particularly at this time, when government agencies are concerned about setting upper limits of exposure in the operating rooms. Unfortunately, there is the question concerning species differences, which does

* McLain GE, Sipes IG, Brown BR, et al: An Animal Model of Halothane Hepatotoxicity Based on Reductive Biotransformation. Abstracts, Annual Meeting of the American Society of Anesthesiologists, 1977, p 481.

make extrapolation from mice to man uncertain. Yet, it is obviously impossible to run these studies in man, and therefore results from other species must be assumed to apply to man as well. After all, the enzymes that carry out the chemical transformations necessary to activate these drugs to react with cellular constituents, thereby producing potential toxic effects, are found in all species. Thus, the anesthetic metabolism will be the same between species, possibly with only quantitative differences.

However, one major difference between man and the species often used for laboratory studies does exist. The latter are usually housed in clean cages with a regimen of proper diet and precise times of light and dark. Any obviously sick animals are removed from the study and destroyed. People, on the other hand, have much more varied health statuses, diets, and other factors that may have profound effects on how a drug is metabolized. For example, an anesthetic concentration of halothane in healthy, untreated animals has no effect. However, halothane administered to animals pretreated with drug metabolism-inducing agents and subjected to low oxygen tensions produces hepatic necrosis. One might question whether physiologic factors might contribute to the development of other toxicities. Assuming this is the case, it makes one shudder at the complexity of the studies necessary to examine this question in relation to mutational changes.

As mentioned previously, a major criticism of some of the work reported to date on the effects of chronic exposure to the anesthetics has been the use of extremely high concentrations. The rationale used by many who use only high anesthetic concentrations is that the effects seen at high concentrations are simply amplifications of what will occur at lower concentrations. This simply is not true. Even in the case of required nutrients, too much can produce toxic effects. Many examples may be cited, including oxygen and vitamin A. Both are required but, at high levels, both produce irreversible toxic effects. Foreign chemicals might be expected to exert some effects at low levels, but these are usually reversible. At higher concentrations the probability of errors in metabolism or alteration in physiologic conditions increases, increasing the possibility of adverse reactions.

Data of the type presented by Wharton *et al.* should not be extrapolated beyond reasonable limits. However, when the results so dictate, as they do in this case, the emphasis should be placed on the safety of the anesthetic drug rather than the toxicity. On the other hand, it should be kept in mind that the lack of effect on fertility and reproduction offers little or no assurance that other effects will appear later in the life of the offspring. This is a totally separate question, and should be kept apart from these studies. It should be borne in mind that any adverse toxic reaction due to halothane is the result of its mebabolism. In studies concerned with reproduction and postnatal survival this metabolism takes place only in the mother, since the fetus does not have the enzymes necessary for the metabolism of drugs. Therefore, any toxic reaction resulting in an effect on fetal development or subsequent adverse effect on the offspring is due to the mother's metabolism.

A very clear, sharp distinction should be made in the studies of possible carcinogenic, mutagenic, and reproductive effects of the volatile agents between chronic exposure and a one-time exposure of the type a patient might receive. This is brought out very nicely in the paper by Wharton *et al.* and by others[2] who have shown neither an effect on reproduction nor teratologic effects in rats and rabbits following short exposures to anesthetic concentrations of halothane.

It seems clear from this study that halothane is probably not the cause of the increased incidence of congenital abnormalities and spontaneous abortions reported to occur in operating room personnel.[3,4] The etiology of these reproductive effects can be identified only by examining all of the agents used in the operating room with carefully controlled experiments designed to show both effective and no-effect levels of exposure.

While it is recognized that the adverse reactions due to the volatile anesthetics need to be studied and understood and at times emphasized, to enable the physician to avoid those conditions that promote such reactions, it should also be remembered that millions of people benefit from the use of the volatile anesthetics. Therefore, more experiments of the type reported by Wharton *et al.* are needed, so that we may consider the safety of the anesthetic agents objectively.

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