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Editorial Views

The Abortive Lives of Modern Inhalation Anesthetics

Readers of this periodical were probably intrigued when, in 1971, almost an entire issue was devoted to studies in volunteers of a new anesthetic, isoflurane (Forane), a novel and useful editorial departure. Since then, a series of reports in the Journal has cast further light on some of the more arcane properties of this heavily fluorinated ether. Why then is this well-studied drug not yet available for clinical use, while its isomer, enflurane, has been accorded official approval? How and when a new anesthetic is released for general use are matters of grave significance for the daily practice of anesthesia.

Some would say that it all began in the late forties, with Robbins' preliminary studies on the anesthetic activities of fluorinated hydrocarbons [1] coming at a time of peak anxiety over the flammability of the available anesthetics. Implying that this was a valid but non-medical reason for finding new agents, Vitcha nicely sketched subsequent developments.[2] Early on, Krantz' industry-supported investigations of a variety of nonhalogenated ethers were followed by the technological improvements essential for the synthesis of fluorinated compounds, opening the gates to a flood of new substances. Although not referable to anesthetics, Samuel D. Cross' remark on textbooks seems germane: "Some fall stillborn from the press, others may die in their infancy, a few attain to vigorous manhood."

First to mature was fluroxene (Fluoromar, 1951), moderately flammable, euphemistically characterized as a useful anesthetic, and now enjoying a limited renaissance. Halothane (Fluothane, 1956) became a great success, not unjustifiably, but as usage widened (by 1967 commanding 68 per cent of the market [3]), the specter of hepatic necrosis loomed. We were then introduced to methoxyflurane (Penthrane, 1960); however, in a comparatively short time its promising career (by 1967, 8 per cent of the market) was cut short by another calamity—nephrotoxicity. Both manifestations, hotly denied at first, their real magnitude still uncharted, may be related to formation in the body of toxic metabolites, an occurrence never dreamed of in the planning stages. Consequently the emphasis in studies by the Stanford group on the liability of isoflurane with respect to renal tubular damage; and the earlier report from San Francisco on its negligible alteration in transport through the hepatic circulation of miniature swine. Except for these threats, anesthesiologists learned to live comfortably with the circulatory and respiratory depressant effects of the initial halogens, using them in balanced methods for the commendable goal of safety.

Just new to the market, where does enflurane (Ethrane) fit into the picture? At a late stage in their explorations, pharmaceutical chemists concluded that the basic ether conformation was the best lead to follow, in addition to avoiding the instability and resulting toxicity from the chlorine and bromine moieties. By this reasoning, enflurane (1963) was conceived. It was rather easily prepared and purified—much more so than its isomer, isoflurane; indeed, the latter was almost abandoned because of the difficulty of synthesis. After testing in lower species (*re* species differences, see the editorial, "Fluroxene and the Penicillin Lesson" [4]), preliminary studies of enflurane in man were authorized. In contrast to the step-by-step procedure elected for isoflurane, there were no broad initial studies on volunteer subjects, a method of anesthetic evaluation so logically set forth by Stevens and Eger.[5] Virtue [6] had already noted in the dog not only an enhanced susceptibility to epinephrine-induced ventricular irritability but a well-defined tendency toward muscle seizures.

Largely of the anecdotal variety, initial reports of the effects of enflurane in man seldom failed to disclose episodes of extraneous muscle movement, and seizures were confirmed by electroencephalography. This heightened irritability has been amply confirmed by the group at Pennsylvania, who showed that the neural effects of enflurane are signified by spontaneous CNS irritability and spike–dome activity upon stimulation of the ulnar nerve, both effects enhanced by increasing depth of anesthesia and hypocarbia. These properties are not shared by isoflurane.

Other observations of note, all in the Journal, include the finding of an increased content of fluoride in the bones of rats pretreated with microsomal inducing agents, then exposed to enflurane; and recovery of fluoride metabolites in the urine of man to the extent of 2 to 4 per cent of the inhaled dose. Circulatory depressant properties are said to result from an action on vasodepressor areas in the medulla, while negative inotropism in the intact canine ventricle is illustrated by a marked decline in maximum force development and rate of development of peak pressure. Effects of *d*-tubocurarine are markedly potentiated. There are no convincing studies on teratogenicity, and effects on the pregnant human uterus have not been described. In short, and in contrast to studies of isoflurane, investigations of enflurane seem unsystematic, incoordinated, and incomplete in respect to many questions that come to mind.

Why then was enflurane promulgated and approved for clinical use? With the apparently safer and more thoroughly studied isomer on the horizon, it is evident that enflurane will be short-lived. We may never even learn the results of an extensive clinical trial; indeed, post-marketing surveillance of a new drug may well be the most revealing aspect of its investigation, as shown by the experience with halothane and methoxyflurane.[7] Tacitly the manufacturer appears to acknowledge all this, for enflurane has been introduced with little fanfare and promotion by salesmen has been lackadaisical. Perhaps the rationale for a brief clinical fling lies in the cost of research and development, as enflurane has been about ten years in the development stage. According to Clymer,[8] the costs of developing new therapeutic agents range from 2.5 to 4.5 million dollars.

Possibly those who now elect to administer enflurane are largely influenced by the agonizing that goes into the selection of halothane in relation to potential hepatic complications. Others have not embraced this anesthetic because of the disquieting possibility of development of seizures in their patients. Furthermore, why go to the trouble of recalibrating the vaporizers now used for other agents or the expense of purchasing new ones. And it may be hypocritical to expect people in training to memorize for an ephemeral compound the chemical formula, MAC value, partition coefficients, vapor pressure etc.—data necessary in an age when anesthetics are given more by calculation than by clinical observation. Finally, is it appropriate for anesthesiologists to cooperate in a venture when instinct and learning suggest otherwise? Thanks to reports appearing in this journal and elsewhere, we have come a long way toward understanding anesthetics, old and new. The perfect anesthetic is not at hand; it may well not be found among the halogenated hydrocarbons or indeed among other inhaled substances.

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