Volume 46, No. 4
April 1977

THE JOURNAL OF Anesthesiology
THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Editorial Views

Anesthesiology
46:233-235, 1977

Is Halothane Hepatitis Chronic Active Hepatitis?

There May Be a Need to Control the Challenge Test

THE ONLY truly compelling evidence for the existence of halothane hepatitis in man—hepatitis caused by halothane in the sense that tuberculous meningitis means meningitis caused by *Myobacterium tuberculosis*[1]—is the existence of two anesthetists[2,3] in whom hepatitis developed after short, deliberate non-clinical exposures to halothane. Supporting evidence stems from a laboratory technician[4] and a nurse anesthetist[5] who had hepatitis and laboratory evidence of hepatic damage, respectively, after occupational exposures to low (pollutant) concentrations of the drug.

Since 1969 it has been widely accepted that the hepatitis that developed after the challenge was caused by the halothane molecule *per se*, or some part of it. However, in 1971, Simpson *et al.*[6] advanced the alternative hypothesis that one of the anesthetists exposed to halothane[3] actually had chronic active hepatitis. They implied that the anesthetist had suffered an exacerbation of chronic active (aggressive) hepatitis that would also have been provoked by the nonspecific stress of a subanesthetic dose of another anesthetic agent. They also implied that any increased incidence of postoperative hepatic damage observed after halothane might result from depression of normal immunologic responses in asymptomatic patients incubating viral hepatitis or having chronic active hepatitis preoperatively. In a subsequent publication relating to the anesthetist, these investigators emphasized that it would not be surprising if factors such as his being aware that his career and perhaps the material well-being of his family depended on the outcome of the challenge had contributed to the nonspecific relapse of the hepatitis.[7] They thus implied that psychic trauma contributed to the exacerbation of the chronic active hepatitis.

Corollaries of the Alternative Hypothesis

Several corollaries stem from the alternative hypothesis. Review of the current status of the four challenged individuals, and of the literature, should provide evidence that will either support or not support the corollaries and, therefore, the alternative hypothesis.

First, if any of the four challenged individuals had chronic active hepatitis when they were challenged, they should continue to show evidence of this usually steadily progressive disease.[8]

Second, if the nonspecific stress of either a short, deliberate non-clinical exposure or an occupational exposure to anesthetic agents can exacerbate chronic active hepatitis within 24 hours, it might be expected that the inordinately greater nonspecific stress of clinical anesthesia and operation would commonly produce a similar immediate exacerbation.

Third, if psychic trauma can contribute to exacerbation of chronic active hepatitis, additional evidence and opinion to support the existence of such "psychosomatic hepatitis" should be available.

Fourth, if the alternative hypothesis is true, one might expect evidence of patients who, having had unexplained hepatitis after exposure to halothane, were found to have chronic active hepatitis, and when exposed subsequently to non-halothane anesthesia were observed to have postoperative hepatitis again.

Fifth, if the alternative hypothesis is true, one might also expect evidence of health-care workers

with chronic active hepatitis in whom hepatitis developed upon occupational exposure to anesthetic agents other than halothane.

Investigation of the Corollaries

Follow-up of the four challenged individuals through personal communications reveals that all four remain in good health, nine, seven, and five years, and 12 months after challenge, and that three have recently had hepatic function tests, with results within normal limits. The physicians who attended the challenged individuals, three of whom had undergone liver biopsy,[3-5] do not believe that their patients have chronic active hepatitis. One of the anesthetists underwent liver biopsy four years after his challenge. This revealed a remarkable regression of the fibrosis and nodule formation that had been seen in the multiple liver biopsies obtained during his illness,[3] while evidence of scarring had developed. The test for HB_sAg (Australia antigen) was found to be negative at the time of the illness in two of the individuals[4,5] and was found to be negative nine years after the challenge in a third. The test was also performed on six stored frozen serum samples taken from the fourth individual during and after his illness, and was found to be negative in each.

One anesthetist left anesthesia immediately after his challenge and went into internal medicine and later, social medicine. The other initially continued his work as an anesthetist but did not administer halothane.[3] During this period a few brief accidental exposures to halothane were not followed by ill effects, but hepatic function tests were not performed. He subsequently also left anesthesia and has now been in general practice for five years. The nurse anesthetist has also given up the practice of anesthesia. The laboratory technician has undergone general anesthesia twice with thiopental and nitrous oxide (the anesthetic machines were pretreated to remove halothane) since her challenge, without mishap, although hepatic function tests were not performed. These data do not support the first corollary of the alternative hypothesis.

There are three reports of the effects of anesthesia and operation in a total of 12 patients who had chronic active hepatitis.[9-11] Ten of the 12 patients demonstrated no evidence of increasing hepatic dysfunction during the first postoperative week, so these data provide little support for the second corollary of the alternative hypothesis.

Exacerbations of chronic active hepatitis often appear to follow a number of factors, including infection and excessive physical activity, in the opinion of some authorities.[12,13] However, as psychic trauma was neither included in these sources nor mentioned in other reviews,[14,15] it appears that the existence of "psychosomatic hepatitis" is not widely accepted. Additional evidence for this is to be found in the fact that physicians responsible for conducting true challenge tests with amitriptyline,[16] aspirin,[17,18] carbenicillin,[19] erythromycin,[20] isoniazid,[21] nicotinamide,[22] paverine,[23] and quinidine[24,25] in a total of 15 patients over the past three years have not controlled the challenge tests by also challenging their patients with a placebo. The individual who had erythromycin-induced hepatitis was challenged with ten different preparations. He had distinct evidence of hepatitis after two of the challenges (erythromycin estolate and propionate), but had a benign course after each of the other eight control challenges (including erythromycin base, ethylsuccinate, gluceptate, and stearate).[20] These data do not support the third corollary of the alternative hypothesis.

In 1972, Simpson *et al.* described four patients whose clinical courses suggest that factors other than halothane can be responsible for repeated episodes of postoperative hepatic dysfunction.[26] Two patients, in whom hepatic dysfunction had developed after halothane, had it again after subsequent non-halothane anesthesia, while in the other two hepatic dysfunction developed on two separate occasions after non-halothane anesthesia. As the clinical courses have not yet been presented in detail, a definitive judgment concerning the scientific importance of this evidence must be postponed, and these data cannot currently be counted as supporting the fourth corollary of the alternative hypothesis.

Finally, although several anesthetic agents have been implicated in postoperative hepatitis, I am not aware of any compelling evidence that health-care workers with or without chronic active hepatitis have a greater than normal risk of development of hepatitis upon occupational exposure to anesthetic agents other than halothane. This fails to provide support for the fifth corollary of the alternative hypothesis.

Comment

Magee has commented that "at any given time, among competing theories, it is the best corroborated theory with the highest information content that gives the best results and is, therefore, or should be, the prevailing one."[27] There is little evidence to support the alternative hypothesis that halothane hepatitis is chronic active hepatitis, and the extent to which one judges the widely accepted hypothesis as corroborated depends upon one's view of the acceptability of the challenge tests as controlled scientific evidence.

Clearly, the circumstances under which both anesthetists were challenged were well controlled in the sense that most of the interfering variables

associated with both an operative procedure and occupational exposure were eliminated. However, the question of the desirability in the future of augmenting such a challenge test with administration of at least another inhalation anesthetic, or a placebo (oxygen), or both, arises. Bunker has recently commented about the two challenged anesthetists, "I have often wondered what would have happened if they had been challenged with cyclopropane rather than halothane. But they were not and therefore we have to live with the data, such as they are."[28] While I believe that there is little evidence to support the need to challenge a health-care worker such as those under discussion with oxygen as a control, it may be necessary to do so because of the skepticism of some qualified observers. On the other hand, there may now be enough general concern that under some circumstances the liver might react nonspecifically to any anesthetic agent to support the need for undertaking a control challenge with an agent other than the one under suspicion.

If the need for such controls should be generally agreed upon, certain practical questions will arise. What specific control anesthetic agent should be chosen in addition to oxygen? Should there be more than one? Should an injectable agent be chosen in addition to an inhalational agent? Should the order of the challenges be randomized? Should the individual be informed that a placebo control is included among the challenges? Should a liver biopsy be performed after each challenge? What immunologic tests should be performed after each challenge, and how specific and sensitive will they be? How long should one wait between challenges?

Answers to these questions may have to be found if there is to be general agreement in the future about the implications of true challenge tests conducted with possibly hepatotoxic anesthetic agents.

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