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Recurrent Hepatitis B-negative Hepatitis after Halothane Anesthesia:

Apparent Failure to Demonstrate Altered Sensitivity

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After 20 years, some anesthesiologists still doubt that halothane hepatitis is a genuine problem, while others, accepting the fact, would attribute the response to altered sensitivity. We report here a clear-cut instance of severe hepatitis following repeated anesthesias with halothane in an obese woman who also had slight hepatic dysfunction following thiopental–nitrous oxide–fentanyl anesthesia. Tests for HB_S (hepatitis B surface) antigen and altered sensitivity to all of the anesthetics given were all negative, while biopsy of the liver revealed no evidence of chronic hepatitis.

REPORT OF A CASE

A 49-year-old white woman was first admitted to Peter Bent Brigham Hospital in December 1967. Medical problems included obesity, adult-onset diabetes mellitus treated with chlorpropamide, and allergies to morphine, meperidine, codeine, penicillin and other antibiotics, all of which caused urticaria. As shown in table 1, she had had many previous anesthesias, including halothane on two previous occasions (1962, 1964), without apparent difficulty. She gave no history of hepatic disease, malaise, recent fever, shellfish ingestion, alcoholism, or exposure to blood products.

On December 2, 1967, the patient was anesthetized for bilateral reduction mammoplasty with thiopental, nitrous oxide, and halothane, and given three units of whole blood. Five-hour operation was uneventful. Fever appeared on the fourth postoperative day, with temperatures peaking at 102 F, and jaundice without skin rash developed on the seventh day, lasting for 13 days. Pertinent laboratory findings included leukocyte counts ranging from 11,700 to 13,700 without eosinophilia, and enzyme elevations indicative of severe hepatic necrosis: SGOT 1,840 IU/l; LDH 2,020 IU/l; bilirubin, total 18, direct 16 mg/dl (table 2). Postoperative medications included pentazocine, phenobarbital, trimethobenzamide and tetracycline, all of which were discontinued after the onset of jaundice. After a diagnosis of drug-induced hepatitis, probably due to halothane, was made, the patient was discharged and warned not to accept halothane again.

A month later she returned for drainage of a mammary abscess. Liver function tests had returned to normal, and she tolerated thiopental and nitrous oxide for the brief procedure (not shown in table 1).

Between 1968 and 1974, several operations were done at other hospitals (details lacking). Following manipulation of an injured knee in October 1972, a 5-minute procedure done with halothane, jaundice appeared on the third day and subsided in two weeks. Peak values relating to liver function then were: total bilirubin 4.6 mg/dl, SGOT 1,544 IU/l, SGPT 1,435 IU/l, LDH 1,124 IU/l, alkaline phosphatase 148 IU/l.

In September 1974, the patient returned to PBBH for exploration of an infected breast. She was obese (height 5'2", weight 212 pounds) and had palmar

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TABLE 1. Anesthetic History

Date	Operation	Anesthetic	Length of Procedure	Prodrome	Icteric	HAA	Transfusion
1946*	T & A	Unknown					
1955*	Thyroidectomy–goiter	Unknown					
1960*	Left salpingo-oophorectomy	Unknown					
1962*	Hysterectomy; salpingo-oophorectomy; appendectomy	Halothane					
1964*	Meniscectomy, knee	Halothane					
1965*	Cholecystectomy	Thiopental, nitrous oxide, d-tubocurarine					
12/67	Bilateral reduction, mammoplasty	Nitrous oxide, halothane	5 hours	No	Yes	Neg.	3 units
10/72*	Manipulation, knee	Halothane	<1 hour	No	Yes	Neg.	No
9/74	Exploration, breast	Thiopental, nitrous oxide, fentanyl	2 hours	No	No	Neg.	No
11/74	Subcutaneous mastectomy	Thiopental, nitrous oxide, Innovar	3 hours	No	No	Neg.	No

* Operations not performed at PBBH.

TABLE 2. Peak Hepatic Abnormalities*

Date	Anesthetic	SGOT* (IU/l)	LDH* (IU/l)	Bilirubin* Total/Direct (mg/dl)	Alkaline Phosphatase* (IU/l)	SGPT* (IU/l)
12/67	Nitrous Oxide, halothane	1,840	2,020	18/16	133	—
10/72	Halothane†	1,544	1,124	4.6	148	1,435
9/74	Thiopental, nitrous oxide, fentanyl	Preop. 68 Postop. 475	406 909	1.5/0.3 0.9/0.4	133 120	— —
11/74	Thiopental, nitrous oxide, Innovar	Preop. 44 Postop. 407	308 643	1.0/0.3	135 123	— —

* Normal values at PBBH:
SGOT 18–70 IU/l
LDH 131–231 IU/l
Bilirubin T/D .1–1.0/.1–.3 mg/dl
Alkaline phosphatase 18–70 IU/l
SGPT < 70 IU/l
† Given at another hospital.

TABLE 3. Results of Immunologic Tests

Test	Result
LE prep	Negative
Latex fixation	Negative
Antinuclear antibody	Trace
Antimitochondrial antibody	Positive XI* Negative XI†
Anti-smooth muscle antibody	Negative
Australia antigen	Negative
Lymphocyte transformation tests	Normal (see text)
Immunoglobulins IgA–IgG–IgM IgE	 Normal Elevated

* Done at PBBH.
† Done at MGH.

erythema, but the liver was normal in size and consistency. The leukocyte count was 12,300 without eosinophilia, SGOT 68 IU/l, LDH 406 IU/l, and alkaline phosphatase 133 IU/l. Following drainage of an abscess, performed with thiopental, nitrous oxide and fentanyl, she seemed well, but SGOT increased to 475 IU/l and LDH to 909 IU/l. In November 1974, a left subcutaneous mastectomy was done, again with the same anesthetics: subsequently slightly abnormal liver function tests were found, SGOT increasing from 44 to 407 IU/l and LDH from 308 to 643 IU/l.

The last two anesthesias (September 1974 and November 1974) were administered in well-ventilated air-conditioned operating rooms where no halothane had been used for at least 12 hours. Vaporizers on the anesthesia machines had been thoroughly drained and the systems flushed with oxygen. Disposable plastic tubing and masks were used to eliminate the possibility of trace amounts of halothane present in the regular rubber tubing used in the breathing circuit.

SPECIAL TESTS

A percutaneous liver biopsy done in December 1974 showed only fatty infiltration, moderate and diffuse, as well as portal fibrosis, mild to moderate, with focal mononuclear-cell inflammation, thought to be consistent with obesity, diabetes and some nutritional component.

Results of a variety of immunologic tests performed during the last admission are shown in table 3. These included tests for evidence of autoimmunity and HB_S antigen and antibodies: all results were negative. The lymphocyte transformation test assays the response of lymphocytes to stimulating antigen as reflected by cell division and measured by incorporation of radioactive thymidine into DNA. Nonspecific stimulation of cell division by phytohemagglutinin or Concanavalin A offers a gross assessment of cell-mediated immunologic competence. Specific antigenic stimulation of lymphocyte cell division is a good index of existing sensitization to many drugs. This patient showed normal responses, that is, stimulation by phytohemagglutinin and Concanavalin A but no stimulation by halothane, fentanyl or a hapten complex of the halothane metabolite trifluoroacetic acid (TFA) with human albumin.

Lymphocyte stimulation was measured after the method used by Paronetto and Popper.[3] Serum was obtained and screened by fluorescent antibody staining for presence of autoantibodies to smooth muscle, mitochondria, and nucleus.[4] Total immunoglobulins as well as individual classes of immunoglobulins were evaluated using standard clinical immunologic procedures.

DISCUSSION

Here was a patient who had major hepatic decompensation following halothane–nitrous oxide anesthesia, and later had less severe hepatic decompensation after the thiopental–nitrous oxide–narcotic sequence. In no instance did extent of change correlate with duration of anesthesia. While earlier the patient might have been anesthetized in a prodromal phase of viral hepatitis, the exacerbations with repeated anesthesias rule out this possibility.[5]

In cases of patients who have putative chronic hepatic disease the possibility of nonspecific aggravation by operation and anesthesia should be ruled out. However, in the case reported herein, negative tests for autoimmunity, and even a liver biopsy without evidence of acute or chronic hepatocellular inflammation and destruction, at the time, do not necessarily eliminate the presence of chronic active hepatitis or any other chronic hepatic disease.

In spite of a history of multiple drug al-

lergies of an IgE-mediated type, there was no sign of hyperreactivity indicative of humoral immunity, such as rash, urticaria or eosinophilia. Performance of the lymphocyte transformation test (LTT) in drug allergy has been more or less established by the work of Halpern *et al.*,[6] yet this test failed to implicate any of the anesthetics given. It should be noted that the LTT has yielded contradictory results[3,7,8] when applied to anesthetics implicated in postoperative hepatitis. Absolute proof of the presence or absence of an immunologic mechanism is difficult to establish. Highly specialized tests, such as measurement of cytotoxic antibodies or lymphocyte-mediated cytotoxicity to liver cells *in vitro* in the presence of halothane, its metabolite, TFA, or fentanyl, could be helpful. In any case, the hard evidence needed to prove a definite allergic reaction is still lacking both in animal models[9] and in man.[8]

HB_sAg-negative hepatitis in the postoperative period may be multifactorial in etiology. We do not know with certainty the relations, if any, among postoperative HB_sAg-negative hepatitis, anesthetics, the stress of operation, and undiagnosed covert chronic hepatic disease. Feinstone *et al.*[10] recently postulated the existence of other infectious agents, still to be identified, causing hepatitis, thus emphasizing the difficulty in identifying a responsible agent. Better tests for hepatitis A should eventually help to clarify the role of this virus in postoperative hepatic failure.[11]

Finally, it is worth noting that obesity in association with fatty infiltration of the liver, as in this woman, may constitute an inherent risk irrespective of anesthetic employed. Young *et al.*[12] have documented enhanced anesthetic biotransformation, with both halothane and methoxyflurane, in obese patients. Eger (personal communication) believes that not only may the metabolites of halothane be hepatotoxic, but that such toxicity is more likely in the obese. Hepatic function may already be impaired, while fatty reservoirs entail a greater uptake and prolonged release at low anesthetic partial pressures. Fractional metabolism of halothane is greater at low partial pressures.[13]

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