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Clinical Workshop

S. G. HERSHEY, M.D., *Editor*

Possible Cross-sensitivity between Halothane and Methoxyflurane: Report of a Case

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In the literature there is one report of a patient apparently hypersensitive to both halothane (Fluothane) and methoxyflurane (Penthrane). This patient, case 9 of Lindenbaum and Leifer,[1] had fever and an abnormal bromsulphalein retention test after halothane, and six weeks later, 11 days after anesthesia with methoxyflurane, died of massive hepatic necrosis. As a result of this case, and on theoretical grounds because of the similarities between the two agents, cross-sensitivity has been discussed and even accepted as fact.[2] Elkington[3] supports cross-sensitivity, but is criticized by Little[4] for basing this speculative conclusion partly on the case of his own patient, who did not receive halothane. Laboratory evidence in favor of cross-sensitivity is seen in the finding by Paronetto and Popper[5] that in two of three patients with halothane hepatitis stimulation of lymphocytes could be demonstrated on exposure to methoxyflurane as well as on exposure to halothane.

The possibility that cross-sensitivity between halothane and methoxyflurane may occur is of particular interest to anesthetists. Many use methoxyflurane instead of halothane to avoid repetitive halothane anesthetization of their patients. Therefore, the following case report is of current interest.

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REPORT OF A CASE

A 55-year-old Caucasian woman weighing 84 kg was admitted to the Royal Alexandra Hospital for removal of a cataract. General medical and surgical history were not significant. The anesthetic history is described below. Physical examination showed the patient to be healthy, though obese, and results of blood tests and liver function tests were normal. The only drug taken by the patient in the preceding six months had been chlordiazepoxide (Librium).

Anesthetic History. In 1939 the patient had had an appendectomy, with unknown anesthetic agents. In 1958, a melanoma had been excised under cyclopropane anesthesia. In 1967, cholecystectomy was performed under halothane anesthesia. Other agents used were meperidine, atropine, thiopental, succinylcholine, gallamine, neostigmine and nitrous oxide. Anesthesia and surgery were uneventful on this occasion, and no blood was given. The patient had a slight fever on the first and second postoperative days, with temperatures reaching 100.4 F (38 C), but it subsided without treatment and she was discharged on the seventh day. The other drugs she had received while in the hospital were aspirin, codeine, propoxyphene (Darvon), carbromal (as Carbrital), and barbiturates. On the thirteenth postoperative day, while at home, the patient developed indigestion and chills, and started to vomit. By the eighteenth day the urine was becoming dark-colored. Jaundice was noticed on the twenty-second postoperative day, and the patient was readmitted with a temperature of 99.4 F (37.5 C) and a tender liver palpable three finger breadths below the right costal margin. Results of labora-

tory studies were: hemoglobin 13.9 gm/100 ml; leukocyte count 16,500, of which 25 per cent were eosinophils; prothrombin time 29 per cent of normal; alkaline phosphatase 24 KA units (normal 4–17); total bilirubin 3.0 mg/100 ml (normal 0.2–1.0). In the next two days the temperature rose to 102 F (39 C), and three days after admission the leukocyte count was 18,300, with 37 per cent eosinophils, and SGOT was 150 mU/ml (normal 10–40). The patient was treated symptomatically with clear fluids by mouth, antipyretics and antinauseants. By the thirty-fourth postoperative day the temperature was normal (and remained so), prothrombin time was 75 per cent of normal; total bilirubin 1.6 mg/100 ml; SGOT 74 mU/ml; leukocyte count 9,800, with 20 per cent eosinophils. On the thirty-eighth postoperative day a liver biopsy was interpreted as showing subacute hepatitis. The patient was discharged to convalesce at home, with the diagnosis of halothane-induced hepatitis.

In October 1969, the patient was admitted to this hospital for the first time, with normal routine liver function tests, for a right cataract extraction, which was performed under thiopental–nitrous oxide–relaxant–scopolamine anesthesia using a semiclosed circle system with CO_2 absorber. Surgery, anesthesia and postoperative course were uneventful and, in particular, postoperative temperatures remained normal. On the day of operation the operating room had been used for three other operations before the patient's, in two of which halothane had been used, and in the third, local anesthesia. In the first case the Jackson Rees modified T piece had been employed, but in the second the circle system had been used for 40 minutes. The anesthetic rubber tubing had been changed but not the baralyme granules or the canister.

Current Illness. A left cataract extraction was done on the day after admission in January 1971. After premedication with diazepam and atropine, anesthesia was induced with thiopental, and after intubation with the aid of succinylcholine, the patient breathed spontaneously with intermittent manual assistance 50 per cent oxygen, nitrous oxide, and methoxyflurane through a semiclosed CO_2 absorption circle system. Anesthesia, the operation (which lasted an hour), and recovery proceeded uneventfully, and the patient was returned to her room. On this day the four patients before her had been anesthetized with halothane, using the same circle system for a total time of three hours. The same absorber and granules were used throughout, but the anesthetic tubing and reservoir bag had been changed after each case. Postoperatively the patient was nauseous, and she was given prochlorperazine (Stemetil). Twenty four hours after termination of anesthesia she had a temperature of 104 F (40 C), with a leukocyte count of 10,700, of which 97 per cent were neutrophils; she received aspirin and ampicillin after blood had been taken for culture. The next day the temperature was a little higher, and the blood was found to have a total bilirubin of 1.3 mg/100 ml, LDH greater than 350 mU/ml, and SGOT greater than 500 mU/ml. There was no rash, arthralgia or eosinophilia, but because clinical and urinary examination, blood culture and chest x-ray showed no evidence of infection, a hypersensitivity reaction to methoxyflurane was diagnosed; prednisone was begun 53 hours after termination of anesthesia in a dose of 15 mg every six hours. Six hours after the first dose the patient felt much better; her temperature was normal, and it remained normal for the rest of her 26 days in hospital. The results of repeated liver function tests over the subsequent weeks are listed in table 1, along with alterations in prednisone dosage. On the sixteenth postoperative day attempted gradual reduction in dosage was abandoned because alkaline phosphatase, SGOT, and LDH levels started to increase again. However, since the patient's discharge from the hospital steroids have been tapered off without evidence of relapse. Blood taken on the nineteenth day was negative for Australia antigen and antimitochondrial antibodies. Only a few eosinophils were ever found in the peripheral blood, and BUN was consistently normal. Liver biopsy was not done because the pathologist anticipated that the histology would have been uninterpretable because of the steroids. To date the patient has been well except for right ophthalmic shingles and an upper respiratory infection three weeks after discharge. She has now fully recovered.

Discussion

Since 1956 there have been many reports of cases of massive hepatic necrosis, usually fatal, following halothane anesthesia. The incidence, etiology, symptoms and signs, and pathology have been described by a number of authors, including Klatskin[2] and Little,[6] who also reviewed all of the reports until 1967 and the various retrospective and prospective studies which had been made. Methoxyflurane has also been incriminated as a cause of postoperative hepatic damage—on ten occasions,[1, 3, 7–13] if case 5 of Peters and others,[14] erroneously included in a halothane series, is counted. The syndrome, pathogenesis, and pathology are thought likely to be the same as those of halothane hepatitis.

Following cholecystectomy in 1968 our patient had most of the clinical, biochemical, and pathologic features which have come to be associated with "halothane hepatitis." She had fever, hepatocellular jaundice, and leukocytosis with very marked eosinophilia. The delay in onset of symptoms for 13 days post-

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TABLE 1. Serial Liver Function Test Results and Prednisone Dosage

	Prednisone (mg)*	Bilirubin (0.2–1.0 mg/100 ml)†	Alkaline Phosphatase (30–85 mU/ml)†	Lactic Dehydrogenase (90–200 mU/ml)†	SGOT (20–50 mU/ml)†
Preoperative	—	0.6	85	160	40
Postoperative day					
2	15	1.3	90	>350	>500
3	80	—	—	—	—
4	60	1.3	165	515	>300
7	30	—	—	—	—
8	30	1.7	160	235	265
10	30	1.8	165	210	260
11	15	—	—	—	—
12	15	1.9	175	190	285
14	15	1.3	190	210	429
16	40	—	—	—	—
17	40	1.8	280	215	450
18	40	2.1	170	185	490
20	40	1.3	160	170	215
22	40	1.4	160	160	165
24	40	1.5	145	65	125
25	30	—	—	—	—
31	10	1.2	125	180	70
33	10	(Discharged from the hospital)			
39	5	—	—	—	—
48	Nil	1.4	95	290	37
56	Nil	1.2	85	165	34

* Total daily dosage.
† Normal values.

operatively is commonly seen when hypersensitivity results from a first exposure to halothane. The histologic picture of subacute hepatitis effectively rules out all causes of postoperative jaundice except infectious, serum hepatitis, and halothane hepatitis. In the absence of a history of exposure to infectious or serum hepatitis, it seems very likely that this illness was a reaction to halothane.

Following the second cataract extraction the patient again developed fever and hepatic damage. Many causes can be excluded with some confidence: preoperative liver function tests were normal; no hypoxia, hypotension or other intraoperative cause was apparent; and the symptoms would not be expected to occur after the other drugs the patient received. There was no history of an occasion when she could have been infected with serum hepatitis, and no Australia antigen (hepatitis-associated antigen[15]) was found. Infectious hepatitis cannot be absolutely excluded, but there was no history of exposure and the subsequent clinical course and response to steroids are not really consistent with it. Therefore, the probability is high that this illness also was related to hypersensitivity to a halogenated anesthetic. This general term is used because, as will be explained, the possibility that the patient received a small amount of halothane inadvertently during the course of methoxyflurane anesthesia cannot be excluded. The diagnosis of a reaction to a halogenated anesthetic is supported by: 1) the history of a previous likely sensitivity reaction; 2) the time relationship between anesthesia and the onset of symptoms; 3) the clinical and laboratory features of the hepatitis which followed; 4) the history of an uncomplicated postoperative course following the first cataract extraction, when no halogenated agent was used.

On the other hand, against the diagnosis are the absences of certain expected features: eosinophilia and other allergic phenomena;

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antimitochondrial antibodies[16]; and death in hepatic coma from massive hepatic necrosis. The absences of these features could be related to the high doses of prednisone, however.

Accepting that the second illness did represent hypersensitivity to a halogenated anesthetic, there are three possible explanations.

The first possibility, *hypersensitivity to methoxyflurane which developed after a first exposure*, is unlikely because of the short time interval between exposure and the onset of the illness.

The second possibility is *accidental re-exposure to halothane*. It is likely that the patient received a small quantity of halothane in association with methoxyflurane anesthesia. There are three possible means of accidental exposure: 1) halothane may be present in measurable quantities in the ambient air of even well-ventilated operating rooms,[17] but once the patient was connected to the anesthetic circuit she would not have been susceptible to exposure from this source. 2) a Fluotec containing halothane but turned to the "off" position was present on the machine when the patient received methoxyflurane; Coulter[18] has pointed out that on some machines fluctuations in the liquid halothane level can be seen during intermittent positive pressure even with the dial turned to "off." Presumably, the valve to prevent back pressure on the Fluotec is absent or not working, and therefore contamination of the fresh gases with halothane is possible. In several of our machines fluctuations have been demonstrated, but not in the one used for this patient. 3) Halothane is taken up by the various anesthetic circuit components during anesthesia.[19] Large amounts are taken up by conductive rubber over a period of hours, and can be transferred to subsequent patients, but since in this hospital all of the rubber circuit parts are changed between cases no halothane transfer can have occurred by this means. Smaller amounts are taken up by baralyme, which becomes saturated in a matter of seconds but takes a longer time to desaturate. It is possible that this patient received a small amount of halothane from this source. The amount of halothane necessary to produce a reaction in a sensitized person is unknown, but from the reports of halothane hepatitis in anesthetists,[20, 21] it is very small. Any halothane this patient received would have come from the baralyme and absorber through which halothane had been passing for three hours immediately prior to her anesthesia. Against this exposure's being enough to explain the hepatitis is the observation that at the first cataract extraction the absorber and baralyme were saturated with halothane, having been exposed to it already for 40 minutes that morning, but no ill effects resulted.

Hypersensitivity to methoxyflurane with a rapid onset of symptoms, the patient already being sensitized to it by virtue of being hypersensitive to halothane, is the third possible explanation. This hypothesis of cross-sensitivity between the two agents would account for the short time lag between anesthesia and onset of illness, and is a much more likely explanation.

Steroids in Hepatic Necrosis. The prognosis for massive hepatic necrosis from any cause is poor, and when hepatic coma follows halothane hepatitis the survival rate may be as low as 7 per cent.[22] The accepted treatments for hepatic coma have been tried: bowel sterilization, intravenous fluids and dietary factors, dialysis, exchange transfusion, and cross-circulation, in addition to the conservative measures used to treat milder hepatitis. Steroids are of little value in infectious hepatitis, but it has been suggested, most recently by Rothberg,[23] that they may be specifically indicated in hepatitis attributed to anesthetics, since this necrosis is believed to follow a hypersensitivity reaction. Klatskin[2] states that in his experience steroids have been beneficial when given before coma developed. However, in the reported cases of hepatitis after halogenated anesthetics, steroids tend to have been given not at all, or late in the course of the disease after the onset of coma, and the patients still have died.

It is impossible to say for certain that steroids were responsible for our patient's recovery, but it seems likely. Symptoms and fever were relieved within six hours of starting prednisone, and the patient went on to recover from a condition associated with a high mortality rate. In addition, the liver function tests tended to deteriorate when the steroid dosage was reduced the first time, but im-

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proved when it was increased again. The absence of eosinophilia, so marked during the "halothane hepatitis," and the absence of antimitochondrial antibodies perhaps also indicate that steroids might have modified the allergic response beneficially.

Conclusions

Uncertainties of diagnosis in this case, and the fact that it is only one case, mean that conclusions must be drawn with reservation. However, it seems permissible to state: 1) there is circumstantial evidence that cross-sensitivity between halothane and methoxyflurane can occur; 2) Sensitivity to these agents is rare. However, when a patient is known to be sensitive to one of them, measures should be taken so far as is practically possible to avoid exposure to either. Strict measures might include using a fresh operating room and an anesthetic machine without halothane or methoxyflurane in it, and segregating the patient in the recovery room from others who have received these anesthetics. More practical measures might be to use a machine only when it can be ascertained that there is no leak of the agents into the anesthetic gases, and to use fresh circuit equipment, including baralyme and ventilator; 3) Steroids may well be beneficial in minimizing hepatic damage from hypersensitivity to halogenated anesthetics. The apparent success of steroids in this case indicates the desirability of giving them early in large doses once a reasonably confident diagnosis of halothane or methoxyflurane hepatitis has been made, without waiting for signs of hepatic failure to appear.

Summary

The case of a patient who developed postoperative hepatitis on two separate occasions is described. The first occurrence followed anesthesia with halothane, a volatile halogenated hydrocarbon, and the second, anesthesia with methoxyflurane, a volatile halogenated ether. An intervening anesthetization involving no halogenated agent was followed by no ill effects. The possible roles of the halogenated anesthetics, of cross-sensitivity between halothane and methoxyflurane, and of inadvertent halothane administration in the production of the hepatitis, are discussed. On the second occasion the patient improved rapidly after the administration of steroids.

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Humidification during Positive-pressure Ventilation of Infants

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When the upper airway is bypassed for prolonged periods by an endotracheal or tracheostomy tube it is essential that means for adequate humidification of the inspired gas be provided. The intact upper airway normally warms the inspired gas to body temperature and saturates it with water.[1] Water content of the inspired mixture is approximately 44 mg/l when it enters the lower airway.

The heated humidifiers and ultrasonic nebulizers generally used with infant ventilators to provide this humidity have been less than satisfactory. To use an ultrasonic nebulizer properly it is necessary to calculate from minute ventilation the nebulization rate needed, and then to monitor the amount of water nebulized. Such measurements are impractical when ventilating infants because both the ventilatory volumes and the quantity of water needed are small. Adjustments for the contribution from the humidity of any ambient air used and for the loss due to fallout in the tubing are also necessary. Frequent measurements would be necessary because even at a fixed setting of the output control, the nebulization rate varies from time to time.[3,4] Finally, when low flows are passed through nebulizers modified for pediatric use to provide low outputs (*e.g.*, Bourns Modification of De Vilbiss Nebulizer Model 350 or 35) the nebulizers become so hot that much of the water is in the form of vapor rather than particles, in part explaining the excessive water deposited in the inspiratory tubing (unpublished observations).†

DEVELOPMENT OF A NEW HUMIDIFIER SYSTEM

For these reasons we consider that an ultrasonic nebulizer is inappropriate for use in mechanical ventilation of infants. Therefore, we have developed a suitable heated humidifier system. The design of such a system must take into consideration certain problems peculiar to the ventilation of infants. First, the volume of air within the system (humidifier and tubing) must be small, to avoid loss of tidal volume due to the compression of gas. Second, the use of small-bore tubing (as demanded by a low system volume) requires that condensation within the tubing be avoided. Finally, the gas must be saturated with water at body temperature when inspired. This is particularly difficult because of the rapid cooling along the tubing with the low minute volumes encountered in ventilating infants. This requirement can be satisfied by keeping the humidifier sufficiently hot to allow for such

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† These considerations may not apply fully when ventilators designed for adults are used for infants. Because of the large "compressible volume" the flow of gas through the humidifier is much larger than the infant's minute volume. This makes volume-limited operation impossible and makes even the estimation of tidal volume difficult.

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