RAPID COMMUNICATION

Halothane hepatitis in Iran: A review of 59 cases

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Abstract

AIM: To study halothane hepatitis (HH) in Iran and its associated risk factors.

METHODS: We retrospectively studied files of all cases diagnosed with HH referred to three referral hospitals and four private centers in Iran from April 1994 to September 2006. Information on age at surgery, gender, medications history, obesity, history of previous exposure, previous reaction to halothane, familial history, type of surgery, perioperative hypoxia or sepsis, morbidity and mortality were recorded and analyzed.

RESULTS: A total of 59 cases were identified. Forty-eight (81%) were women. The median age at the time of surgery was 44 years (range, 18 to 80 years). Sixty percent of patients were above 40-year-old. Obesity was observed in 22.2%. Previous history of exposures to halothane was noted in 61% of which 50% had history of post-exposure reaction. Coronary artery bypass graft (CABG), cholecystectomy, and cosmetic surgeries (mainly weight reduction) were the most frequent surgeries. The mortality rate was 12.2%. In patients developing encephalopathy, it was as high as 50%.

CONCLUSION: HH remains an important cause of morbidity and mortality in centers still using this anesthetic. However, a large percentage of these cases could have been avoided. To lessen occurrence of further cases of HH, the authors suggest that in female patients having a history of surgery (or delivery) with general anesthesia, the use of halothane should be absolutely avoided. Utilization of proper substitutes in adults' anesthesia is advocated.

INTRODUCTION

Halothane was first introduced to clinical practice in 1956 and was immediately recognized as a great advance in anesthesia[1]. First reports of postoperative liver necrosis with halothane began to appear in 1958[2,3] followed by further anecdotal reports[4-7]. By 1963, 7 years after the introduction of halothane, at least 350 cases of "halothane hepatitis" (HH) had been reported[8]. These reports led to the National Halothane Study, which estimated fatal hepatic necrosis following halothane anesthesia to be approximately 1 in 35 000 in the US[9]. Other retrospective studies confirmed that halothane was associated with severe liver dysfunction, with an incidence ranging from 1 in 6000 to 1 in 35 000[10].

Two major types of hepatotoxicity are associated with halothane administration: type I (mild) and type II (fulminant). Type II hepatotoxicity is associated with massive centrilobular liver cell necrosis that leads to fulminant liver failure and is clinically characterized by fever, jaundice, and grossly elevated serum transaminase levels. It appears to be immune mediated and initiated by oxidative halothane metabolism by cytochrome P450 to an intermediate compound. This compound binds to trifluoroacetylate proteins in the hepatic endoplasmic reticulum, thought to occur in genetically predisposed

individuals[11]. In this study, type Ⅱ hepatotoxicity was regarded as HH.

Concerns about its hepatotoxicity have virtually eliminated the use of halothane for adults in the United States and many other countries. Halothane was eventually replaced by safer newer volatile anesthetics such as isoflurane[12,13]. But in other countries with different medicolegal climates, halothane is still widely used because of its relatively low cost[11]. There are reports of HH from South Africa[14], Tunisia[15], Kenya[16], India[17], and Spain[18]. Halothane is being used as the main anesthetic in more than 80% of hospitals of Iran[19]. Unfortunately, increasing numbers of HH are being reported in Iran. In this retrospective study, we review cases reported within a 12-year period from 7 centers in Iran.

MATERIALS AND METHODS

Cases were recruited from three referral hospitals (Namazi Hospital of Shiraz University of Medical Sciences, Shariati Hospital of Tehran University of Medical Sciences, Mehr General Hospital of Tehran) and four referral GI clinics in Tehran, from April 1994 to September 2006.

There is no definite test for the diagnosis of HH and it is basically a diagnosis of exclusion. In our study, the diagnosis of HH was confirmed if the patient met the following criteria; clinical findings (jaundice, malaise), paraclinical findings (marked elevation of ALT, AST, total and direct bilirubin), recent exposure to halothane, exclusion of other causes of liver damage (viral hepatitis, *etc*) and confirmation by at least one gastroenterologist as fulminant HH.

Charts were reviewed to determine the age at surgery, weight, gender, medication history (including P450 inducing drugs), preoperative obesity (BMI ≥ 30), history of recurrent exposure to halothane, history of previous reaction to halothane (unexplained post-operative fever, jaundice, abnormal liver enzymes following earlier halothane anesthetics), positive family history (defined as reactions to halothane in first degree relatives), type of surgery, perioperative hypoxia, interval between anesthesia with halothane and symptoms heralding or attesting hepatitis, postoperative sepsis, morbidity and mortality.

Data were presented as simple count and percent, median and range, or mean ± SD and were compared by Fisher's exact test. Statistical calculations were performed using SPSS version 15.0. $P < 0.05$ was considered significant.

The study was approved by the institutional review board and ethics committee of the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences.

RESULTS

Fifty-nine cases of HH were identified, 48 women (81%), 11 men (19%). The median age at the time
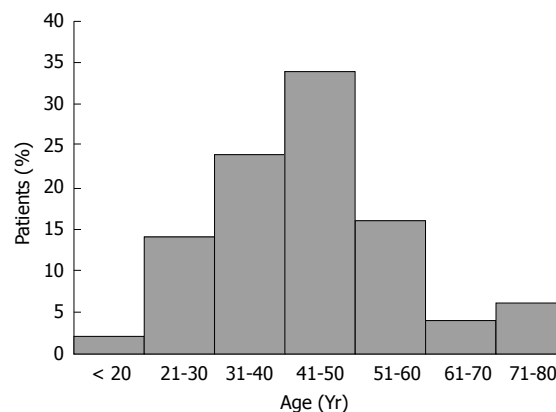

Figure 1 The age distribution of patients with HH.

Table 1 Characteristics and laboratory test results of 59 patients with HH

Variable	*n*	%
Characteristics		
Female gender	48	81.4
Obesity	6	22.2
Recurrent exposure history	22	61.2
Post-exposure reaction history	10	17
Encephalopathy	8	14.5
Requiring ICU care	7	12.5
Mortality	6	12.2
Laboratory test results		
ALT rise	48	100
AST rise	47	97.9
Total bilirubin rise	41	97.6
Direct bilirubin rise	37	100
Alkaline phosphates rise	35	100
PT rise	21	61.8

Percentages are relative to patients for whom data was available.

of surgery was 44 years (range, 18 to 80 years). Sixty percent of patients were above 40 years old. The age distribution of patients is given in Figure 1.

The mean of interval between anesthesia and hepatitis symptoms was 15.2 ± 13.6 d. The mean weight of patients was 76.1 ± 18.7 kg and 22.2% of patients were obese. Data on clinical findings, morbidity, and mortality are given in Table 1. No cases had previous history of liver disease or sepsis. One case had documented perioperative hypoxia, another one had a positive family history of HH, and two others had positive drug history (Phenobarbital). Table 1 shows the results of routine laboratory investigations including biochemistry and coagulation tests.

Coronary artery bypass graft (CABG), cholecystectomy and cosmetic operations (mainly weight reducing surgeries including partial gastrectomy and liposuction) were the most common operations. Information about different types of surgery is given in Table 2. The mortality rate was 12.2%. In patients who developed encephalopathy, it was as high as 50%. The mortality rate in male patients was higher than females (20% *vs* 12%), although this did not reach statistical significance.

Table 2 Surgery types and the percentage of cases of HH regarding each type of surgery

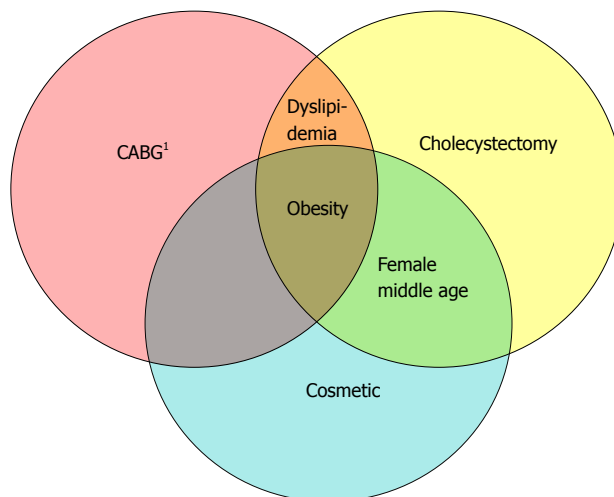| Variable	n	%
Cholecystectomy	5	8.5
CABG surgery	4	6.8
Aesthetic surgeries		
Partial gastrectomy	1	1.7
Liposuction	1	1.7
Face lifting	1	1.7
Mandible reconstruction	1	1.7
Others	3	3.4
General Surgeries		
Intra-abdominal surgeries	2	3.4
Extra-abdominal surgeries	4	6.8
Obstetrics & Gynecologic surgeries		
Cesarean section	2	3.4
Others	9	
Eye surgeries	3	5.1
Orthopedic surgeries	2	3.4
Urologic surgeries	2	3.4
Other types of surgery	5	8.5

Percentages are relative to patients for whom data was available.

Figure 2 Common risk factors between three most common surgeries among patients with HH. [1]Coronary Artery Bypass Graft Surgery.

DISCUSSION

Because of the retrospective nature of the study, confirmation of the diagnosis with antibodies to halothane-altered protein antigens was not possible.

It has been shown that HH is more frequent in females, male-to-female ratio ranging from 1:1.6[11] to 1:2[20,21]. In our series, this ratio was 1:4.3. Additionally, it has been revealed that middle-aged patients have a greater propensity to develop liver damage than the young or elderly[11, 21-24]. Over 70% of patients are more than 40 years old with peak age of 50-60[10]. We also observed a greater prevalence among middle-aged patients, yet it appears that the patients in our series are younger compared to other series[14]. The younger age of our patients could be due to the fact that the most common surgery in our series, cholecystectomy, is frequently performed in young to middle-aged women. Obesity appears to be the common factor between most frequent operations associated with HH in our series. CABG, cholecystectomy and weight reducing-cosmetic surgeries are all linked with obesity (Figure 2). It has been showed that hepatic dysfunction is more common in obese than in non-obese patients[23-25]. As halothane accumulates in adipose tissue, this could delay its excretion and, theoretically, prolong exposure to potentially reactive halothane metabolites, resulting in increased risk in obese patients. In addition, obese patients metabolize halothane more extensively than do non-obese patients[26], further predisposing them to liver injury.

Other possible relationships between the most common surgeries are shown in Figure 2. Female gender and middle age are common risk factors for gall stone formation, cholecystitis, and coronary artery disease[27-30]. Dyslipidemia is also a risk factor for coronary artery disease and plays an important role in the pathogenesis of gallstones[27,28]. Furthermore, hypoperfusion is the possible explanation of hepatic injury in CABG and cholecystectomy surgeries. Imbalance between oxygen supply and demand predisposes the patient to halothane-induced liver damage[10,31]. Halothane has been shown to decrease both portal blood flow and hepatic arterial blood flow[32-35]. Furthermore, surgical manipulation of the splanchnic bed may reduce hepatic blood flow[36]. It has been demonstrated that CABG is accompanied with splanchnic hypoperfusion and hypoxia[37,38]. The ischemia is probably caused by hypoperfusion due to low cardiac output, hypotension due to blood loss, and intra-abdominal atheroemboli. As a result, ischemia may be the common mechanism of predisposing the patients to the HH in CABG and cholecystectomy surgeries.

Multiple exposures to halothane are the single greatest risk factor for HH[11]. The association between hepatotoxicity and repeated exposure to halothane might be explained by the fact that halothane anesthesia itself induces drug metabolizing enzymes[39-41]. The risk of HH is increased greatly when repeated halothane anesthetics are given over a short period[11,22,42,43], especially at intervals of < 6 wk[11]. In the present study, previous history of exposure to halothane was noted in 22 of 36 (61.1%) and obvious post-exposure reaction history in 10 of 22 (45.5%). Considering the fact that guidelines clearly elucidated that patients with previous reaction to halothane are among the high-risk groups[44] and should have not received halothane again, in addition to the results of this study, it is concluded that a large percentage of these cases could have been avoided. To lessen further occurrence of cases of HH, we suggest that the use of halothane in patients who are at risk of HH should be absolutely avoided. This group of patients consists of female patients having a history of post-anesthesia reactions following exposure to halogenated anesthetics. On the other hand, the item of "post-exposure reaction history" is often quite difficult to obtain with a reasonable certainty; therefore, its usefulness in preventing HH should be weak. As a result, a second set of criteria, which is female gender patients with a history of surgery (or delivery) with general anesthesia, is recommended. This is likely easier

to obtain and can be simply defined pre-operatively by the anesthesiologist *via* reviewing the "anesthesia sheet" of the previous general anesthesia. Strict adherence to this set of criteria will reduce, but not totally prevent, further cases from occurring in countries still utilizing halothane in adults' anesthesia.

Furthermore, the incidence of liver injury was greater in subjects treated with phenobarbitone before halothane anesthesia than in those not taking enzyme inducing medication[11,45]. There were two cases of chronic Phenobarbital use in our series among the 16 for which data was available.

Susceptibility to HH may be heritable and positive family history must be taken into consideration[11,46]. We had one case with positive family history of HH out of 7 cases that had data.

Type Ⅱ hepatotoxicity has a mortality rate of approximately 50%, which rises to 80% when hepatic encephalopathy is present[10,11,31,47]. Our data confirms this since the mortality was 50% in our patients with encephalopathy. Such patients have a very poor prognosis and should be referred to specialist centers where orthotopic liver transplantation is available[48]. Patients who survive the acute illness usually make a complete recovery[11]. Considering that none of our patients underwent liver transplantation, our mortality rate is considerably lower than other reports[14]. Improved intensive care, faster diagnosis and initiation of medical care may be involved. In consistence with former reports[22,24,49], mortality in male patients was higher than females in our series (20% *vs* 12.1%), although it did not reach statistical significance.

Although halothane is rarely associated with fulminant hepatic failure[48], it occupies the fifth place of suspected hepatic adverse drug reactions with a fatal outcome received by the WHO Collaborating Centre for International Drug Monitoring in Uppsala Sweden from 1968 to 2003[50]. Consequently, its usage was restricted in adults' anesthesia; however, it is still widely used in many countries, including Iran, mainly due to economic reasons[11].

Guidelines have been developed to reduce the probability of a patient developing HH; still, adverse reactions continue to occur. Even though it was clearly noted in guidelines that patients thought to be sensitized to halothane must never be re-exposed to the drug, we found ten cases of known previous reaction that were re-exposed to halothane. Based on the results of this study, to lessen further cases of HH to occur, the authors suggest that in female patients having a history of surgery (or delivery) with general anesthesia, the use of halothane should be absolutely avoided. However, the most effective preventive tool is to avoid the use of halothane in adults' anesthesia. Utilization of proper substitutes is advocated.

ACKNOWLEDGMENTS

COMMENTS

Background
Halothane is a volatile anesthetic, which was first introduced to clinical practice in 1956. After several years, concerns about its hepatotoxicity have virtually eliminated the use of halothane for adults in the United States and many other countries. It was replaced by safer newer volatile anesthetics such as isoflurane. However, in some countries with different medicolegal climates, halothane is still widely used because of its relatively low cost. In Iran, halothane is being used as the main anesthetic in more than 80% of hospitals. Unfortunately, increasing numbers of halothane hepatitis (HH) are being reported in Iran.

Research frontiers
Although the use of halothane was restricted in many countries, there are reports of HH occurring in South Africa, Tunisia, Kenya, India, and Spain in recent years.

Innovations and breakthroughs
In previous studies, guidelines have been developed to reduce the probability of a patient developing HH; however, the results of this study revealed that they are largely ignored in Iran. Furthermore, the results showed that a large percentage of these cases could have been avoided. In this study, we aimed to suggest a set of criteria that can easily define the high risk group of patients pre-operatively.

Applications
To reduce, but not totally prevent, further cases of HH from occurring in countries still utilizing halothane in adults' anesthesia, the authors suggest that the use of halothane should be absolutely avoided in female patients with a history of surgery (or delivery) with general anesthesia. However, the most effective preventive tool is to avoid the use of halothane in adults' anesthesia. Utilization of proper substitutes is advocated.

Terminology
Two major types of hepatotoxicity are associated with halothane administration: type Ⅰ (mild) and type Ⅱ (fulminant). Type Ⅱ hepatotoxicity is associated with massive centrilobular liver cell necrosis that leads to fulminant liver failure and is clinically characterized by fever, jaundice, and grossly elevated serum transaminase levels. In this study, type Ⅱ hepatotoxicity was regarded as HH.

Peer review
This series of 59 cases of HH collected in 12 years in a country with health security conditions lower than those found in the US or Western Europe is of high medical interest for the Iranian population and populations of other countries in the Middle East and, most likely, also in Africa and Asia. Therefore, the topic of the present paper is quite pertinent and extremely interesting for many physicians around the world.

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