Journal of Basrah Researches ((Sciences)) Volume 37. Number 4 A / 15 August ((2011)) **84-92**

Effects of halothane anesthesia on patients with abnormal liver function tests

ISSN –1817 –2695

Wafaa A.N.Fleifel
Dep. of Pharmaceutical chemistry, pharmacy College,University of Basrah, Basrah, Iraq

((Received 24/11/2010, Accepted 8/6/2011))

Abstract

This study done randomly in Basrah General Hospital during the period between March to December 2006, Forty five patients (age range 6 -75 years), (21) 46.8% males and 24 (53.2%) females, for evaluating of the safety and laboratory data for halothane anesthesia, all of them presented with mild abnormal liver functions during routine investigations to elective surgeries under general anesthesia (the common use of halothane known to cause hepatotoxicity). Five milliliters from venous blood were taken before the operation then immediately after the operation, and on the first and third day postoperatively. Blood was tested for serum transaminases, alkaline phosphatase and total bilirubin, using appropriate kits. Twenty two (48.89%) had repeated exposure to halothane by underwent previous surgeries, and 23 (51.11%) are newly exposed to halothane. No significance change had been observed in relation to the gender of the patients for all parameters. None of the patients showed severe changes in each type of the parameters when analyzed individually (more than 3 times their upper normal limits). We conclude that laboratory values immediately after surgical operations and for 3 days later have no trend for a major derangement in the patients with abnormal liver functions.

Key words: Halothane anesthesia, liver functions, abnormal function tests.

Introuctiion

Halothane is (Fluothane) inhalational aneasthetic agent, it is a hydrocarbon molecules (trifloro-bromo-chloroethane) have a formula C2F3HBrCl. Introduced in 1956, were the first of the modern, and halogenated inhalational anesthetics used in clinical practice. It is a potent agent that is used for maintenance of anesthesia. [1] Halothane is the anesthetic most studied regarding possible hepatotoxicity Figure (1). In absence of previous hepatic dysfunction related to halothane there is no contraindication for the use of this anesthetic in the presence of liver disease. [2, 3] Postoperative liver dysfunction has been associated with most volatile anesthetic agents from diethyl ether on word, but in recent years halothane has received the most attention [4]. A direct effect of the drug or its metabolites is believed to be responsible in part for halothane-associated hepatitis. [5] It is now clear that all individuals exposed to halothane metabolize halothane to TFA-halide and thereby produce labeled proteins, but why only some patients develop liver damage after halothane anesthesia while millions of others have been exposed to the drug, many of them repeatedly without apparent ill effect, it is still not known. Metabolism of halothane appears to be under genetic influence in both guinea pigs and humans, and rare reports have appeared claiming halothane hepatitis in patients who were related. [5] The most practical way of reducing the incidence of halothane hepatitis is almost to take a good history of previous Figure (1) [5]

Mechanism of TFA and Br formation from P450-catalyzed halothane oxidation

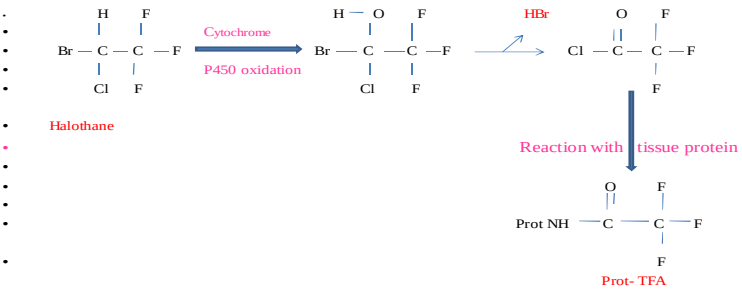

Diagram of metabolic pathways for halothane: Oxidative metabolic products after interaction with cytochrome P450; generation of protein TFA molecules which may be responsible for an immunological response and cross reactivity

anesthetic exposure. In addition, the introduction of enflurane and isoflurane was another reason for the decline in the use of halothane and the potential absence of hepatotoxicity resulting from their lesser metabolism than halothane was an important point in promoting their use as alternatives. [6] Halothane, at the present time is widely used as inhalational anesthetic in Basrah, and at times is the only one. This has made a good opportunity to investigate its effect on abnormal liver function tests in our local patients who are exposed to it. In addition, drugs like analgesics and antibiotics are, also, heavily used particularly in the postoperative period. Several of these drugs can compromise liver functions. All these factors form the basis for conducting the present study. The tests used to detect and assess hepatocyte injury are based on measurement of cellular contents that have leaked into the circulation. [7] Biochemical assessment of liver dysfunction during and after anesthesia usually includes measurement of plasma or serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) activity as well as alkaline phosphatase (ALP) [8], that have been expressed on the relevance of increases in AST and ALT activity in the diagnosis of anesthetic–induced liver damage [7]. The aim of present study was to estimate the effect of halothane anesthesia and postoperative drug administration's on liver function tests in the patients with the abnormal liver function tests.

Patients and Methods

In Basrah General hospital during the period between March to December 2006, (45) patients with mild abnormal elevated liver function[an elevated of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP)] underwent surgical operation under general anesthesia using of

halothane 1-3 % v/v in 100% oxygen for different times of exposure (ranged 10-180 minutes). Anesthesia was induced by 6 mg/kg body mass thiopentone 2.5 % intravenously (i.v) and endotracheal intubation was facilitated with (i.v) injection of 1 mg/kg of succinylcholine; then muscle relaxation maintained by (i.v) pancuronium 0.1 mg/kg body mass. At the end of the surgery residual muscle relaxation was reversed using neostigmine 2.5 - 5 mg (i.v) mixed with atropine 1.5 mg in the same syringe. Monitoring during anesthesia for vital signs includes indirect arterial blood pressure, pulse rate, oxygen saturation by pulse oximetry and electrocardiographic monitoring.

These patients had different types of surgical operations and they were receiving different regimens of antibiotic and analgesic drugs. A follow-up form was filled for each patient. This includes name, age, gender, type of operation, occupation, as well as medical history for any previous illness and type of treatment, and for any previous surgical operation.

After an average preoperative fasting for 6-12 hours, venous blood samples (5 ml) were taken by a sterile disposable syringe then collected in plain plastic tubes in the following time intervals; immediately before (control) and after operation(at recovery room) and then followed-up at the 1st and 3rd postoperative days.

The serum was separated immediately after withdrawal and stored in refrigerator at -4°C. until analyzed, and was investigated for different parameters of serum levels for liver function tests by using diagnostic kits which include: [Aspartate aminotransferase kit AST Randox No.147 (normal range7-20 U|l) [8], alanine aminotransferase kit ALT Randox No.146 (normal range 7-20 U|l) [8], alkaline phosphatase kit ALP BioMeieux No. 61511 (normal range 3-13 U|100ml) [9], bilirubin kit Human No. 10012 (normal range up to 1mg|dl) [10]]. These patients had different types of surgical operations and they were receiving different regimens of antibiotic and analgesic drugs.

Due to unavoidable circumstances, not all the parameters were estimated that is because some patients were discharged one or 2 days after operation.

Data were analyzed statistically using SPSS computer package, version 11.

ANOVA and paired t-test were used to test the significance of results. $P < 0.05$ was taken to be the lower limit of significance.

Results

Characteristics of the patients in this study are shown in (Table 1).

(Table 2) shows frequency of halothane exposures for patients in previous surgeries, 48.89% (22) had repeated exposure to halothane by underwent previous surgeries and 51.11 % (23) are newly exposed to halothane in the study period.

There was statistically significant changes ($P<0.05$) in sAST levels in the 1st and 3rd days postoperatively respectively compared with the preoperative level, it changes from (30 to 20.5 and 22.8 U/l) respectively (Table 3).

There were a statistically significant differences for sALT and serum t-bilirubin levels ($P<0.05$) only at immediately postoperatively, it changes from (27.6 to 20.4 U/l) in relation to sALT levels and from (1.75 to 0.86 mg/dl) in relation to serum t-bilirubin levels (Table 3).

There was statistically significant change ($P<0.05$) in sALP levels at immediately, 1st and 3rd days postoperative periods respectively compared with the preoperative level, it changes from (24.4 to 21.3, 16.7 and 17.8 U/100ml) respectively (Table 3) .

There was not statistically any significance observed for male and female patients over 3 days follow up period, also no significant differences between them were seen

(Table 4) .

Table (1) Patients characteristics

Patients characteristics		No.	%
Age Total age range (6-75)years	Mean age(34.8± 16.1)years	45	100
Gender	Males mean age (31.9±16.8) years	21	46.8
	Females mean age(37.1±15.4) years	24	53.2
Type of surgery	Liver hydatid endocystectomy	10	22.22
	Laparoscopic cholecystectomy	6	13.33
	Stomach	3	6.66
	Exploratory laparotomy	10	22.22
	Thyroidectomy	2	4.44
	Upper & lower limbs	14	31.11
Duration of halothane exposure range (10-180) minutes	<60	7	15.6
	60-120	25	55.6
	>120	13	28.8
Smoking habits	Smoker	10	22.22
	Nonsmoker	35	77.78

Table (2) Frequency of halothane exposures in previous surgeries

Frequency of halothane exposures	No. of patients	*%*
0	23	*51.11*
1	11	*24.44*
2	3	*6.67*
3	6	*13.33*
4	2	*4.45*
Total	45	*100*

Table (3) Changes in liver function tests for patients with abnormal liver diseases at perioperative period

mean± SD (n)

Liver function tests	Immediately pre-operative period	Post–operative periods		
		Immediately	1st day	3rd days
sAST (U/l)	30.0 ± 8.07 n=16	25.2 ± 16.4 n=16	20.5±11.5 * n=11	22.8 ± 11.0 * n=8
s ALT (U/l)	27.6 ± 6.6 n=13	20.4±5.2 * n=13	20.5±10.3 n=8	16.0± 11.0 n=6
sALP (U/100ml)	24.4±11.3 n=43	21.3±13.2* n=43	16.7 ± 7.3 * n=31	17.8±4.3* n=19
t-Bilirubin (mg/dl)	1.75 ±0.6 n=13	0.86 ±0.4* n=13	1.84 ±1.5 n=8	1.43±0.3 n=5

* P <0.05; sAST= serum aspartate aminotransferase normal range (7-20 unite / litre); sALT= serum alanine aminotransferase normal range(7-20 unite / litrel); sALP= serum alkaline phosphatase normal range (3-13 unit|100ml); t-Bilirubin= total bilirubin normal range(up to 1mg|dl); SD =standard deviation; (n)= number of patients

Table (4) Changes in liver function tests for males (M) and females (F) liver diseases mean ± SD (n)

Liver function tests Males & Females		Immediate pre-operative period	Post–operative periods		
			Immediately	1st day	3rd days
s AST (U/l)	M	30±8.3(11)	27.4±16.9(11)	23.5±11.8(6)	17.8±11.3(5)
	F	29.5±9.1(5)	13.0±4.2(5)	11.5±2.1(5)	7.0±1.8(3)
s ALT (U/l)	M	27.8±6.2(10)	20.3±5.7(10)	25.1±9.6(6)	26.7±13.8(4)
	F	27.2±8.5(3)	20.7±4.6(3)	12.5±6.3(2)	15±1.4(2)
s ALP (U/100ml)	M	22.9±6 (22)	20.8±12.3(22)	18.4±6.8(11)	17.4±5.8(7)
	F	25.5±13.9(21)	21.7±14 (21)	17.4±5.8(20)	18±3.6(12)
t-Bilirubin (mg/dl)	M	1.96±0.4(10)	0.99±0.4(10)	2.0±1.7(6)	1.4± 0.3(4)
	F	2.24±0.4 (3)	0.92±0.9 (3)	1.25±0.6 (2)	1.0 (1)

sAST= serum aspartate aminotransferase normal range (7-20 unite / litre); sALT= serum alanine aminotransferase normal range (7-20 unite / litrel); sALP= serum alkaline phosphatase normal range (3-13 unit|100ml); t-Bilirubin= total bilirubin normal range(up to 1mg|dl); SD =standard deviation; (n)= number of patients.

Discussion

Halothane, enflurane, and isoflurane, have been associated with jaundice, hepatitis, and death. Hepatotoxicity associated with halothane is the most common, and has been studied extensively. Halothane produces two types of hepatotoxicity. The first is a mild form seen in 20% of patients given halothane anesthesia [5] and is characterized by nausea, lethargy, low grade fever, and mild transient elevations in liver amino transferase enzymes (ALT, AST), and sometimes, transient jaundice with low morbidity. In contrast, a fulminant hepatic necrosis (halothane hepatitis) occurs in approximately 1/20,000 adult patients exposed to halothane and is characterized by markedly increased serum ALT, AST, and bilirubin concentration, hepatomegaly, hepatic encephalopathy, jaundice, and, often, death [11]. The predominant histologic feature is acute hepatitis with centrilobular necrosis. A variety of risk factors have been identified, which are commonly associated with halothane hepatitis. These include obesity, female gender, middle age, and having multiple anesthetics over a short period [12,13]. Compared to adults, relatively few cases of halothane hepatitis have been reported in children [14,15].

More recently, increased plasma concentration of glutathione-s-transferase (a sensitive and specific index of acute, drug-

induced, hepatocellular dysfunction) has been demonstrated after halothane but not after isoflurane anesthesia. [16] These studies also showed that halothane is associated with less liver damage when given under high (100%) oxygen concentration. Subclinical form of liver dysfunction could be caused by toxic products of halothane metabolism, possibly influenced by genetic and pre-existing enzyme factors [17] or by hepatic hypoxia in relation to oxygen demand. [18]

Partly as a result of a perceived threat of litigation in relation to hepatic damage, the use of halothane is declining in many parts of the world[18], and it has even been suggested that the agent is "obsolete"[19, 20]. Others have challenged this view, arguing that, as most cases of halothane-associated hepatitis are benign and fulminant hepatic failure is extremely rare, these problems should be viewed in the context of other outcomes, particularly respiratory depression and effects on coronary artery blood flow that may occur when alternative anesthetic agents are used. [21- 23]

Other studies, Case reports of fulminant hepatic failure after halothane anesthesia, often showed a history of recent previous exposure to halothane. [24]While another case of acute cholestasis hepatitis following exposure to the inhalational anesthetic isoflurane; 3 weeks following repair of the right rotator cuff under general anesthesia, there was no evidence for viral, autoimmune, or metabolic causes of hepatitis. No other medications were involved except for dipyrone for analgesia. The clinical and histological picture of this case resembles halothane hepatitis. [25]

Wark *et al* [26] found that only 9.6 % of the absorbed halothane was metabolized to TFA. This indicates that mild degree of liver disease did not decrease the ability of the liver to biodegrade halothane via oxidative pathway.

The currently available i.v. anesthetics appear to be devoid of hepatotoxic potential. [27] Drugs may have important toxicity in patients with underlying liver or kidney disease. [28] However, non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with hepatotoxicity in susceptible patients. In view of the very large recipient population, the incidences of induced liver injury have been found to be rare (approximately 0.1 per 100,000 patients treated). [29]

Our results in patients with mild abnormal liver diseases who receive halothane anesthesia were 1-3 % v/v in 100% oxygen. No significance change had been observed in relation to the gender of the patients for abnormal liver diseases. The decreases of liver functions tests postoperatively may be due to the removal of the causes of liver disorder or treatments of patients by surgery like liver hydatid cyst removal or laparoscopic cholecystectomy. Individually, none of the studied patients exceeded the 3-fold increases in the upper normal values of each test.

There now seems to be an agreement with those other results in patients with chronic hepatic and renal disease who received either isoflurane or desflurane , within either liver or renal disease groups, each inhaled anesthetic was administered at MAC equivalencies, there were no changes in already abnormal laboratory values with either anesthetic within both chronic disease groups.[30]

The laboratory values at immediately after surgical operations and for 3 days later, there was no trend for a major derangement for patients with mild liver disease. This also agrees with the previous study conducted for patients with normal liver function tests that have been also exposed to halothane anesthesia. [31]

Conclusion

We conclude the halothane anesthesia has no clinically significant effect on liver function tests in the patients with mild abnormal liver diseases.

ACKNOWLEDGEMENTS

I would like to express my great thanks to Dr. Hamid Abdul-Nabi Flaifel, consultant anesthetist at Basrah General Hospital for allowing access to his patients, his support and help; and all the staff those working at operation theatres 2 and 3 in Basrah General Hospital.

References:

1. S. Alex, C. Evers, Michael Crowder and R.Jeffrey Balser. General Anestheticss. In: The pharmacological Basis of Therapeutics. 11th ed. Toronto: McGraw. Hill Company. 2006: 354-363.
2. K. Robert Stoelting, M.D. Indianapolis, IN. Anesthesia and the patient with liver disease. Anesthesiology Online .J .2003.
3. S. Gelman. Anesthesia and the Liver. In: PG Barash, BF Cullen, RK Stoelting, eds. Clinical Anesthesia. Philadelphia. Lippincott-Raven. 1997:1003-24
4. EJ Frank. and BR. Brown . Postoperative hepatic dysfunction. Balliere's clinical Anaesthesiology 1992; 4: 931-520.
5. Elliott, R.H. and Strunin. Hepatotoxicity of volatile Anaesthetics. Br J Anaesth. 1993; 70: 339-48.
6. JM. Neuberger, Halothane and the implications of hepatitis. In: L. Kaufman ed. Anaesthetics review, 8. London: Churchill Livingstone, 1991;179-94.
7. Robert Dufour and D. Evaluation of liver function and injury. In: Clinical diagnosis and management by Laboratory Methods, 20th ed. Toronto: W. B. Saunders Company. 2001: 246-273.
8. N. W. Tietz. Text book of clinical chemistry, 3rd ed C.A. Burtis, E.R. Ashwood, W.B. Saunders 1999 :652-657.
9. A. Belfield and D.M. Goldberg – Revised assay for serum phenyl phosphatase activity using 4-amino-antipyrine Enzyme, 1971,12, 561-573.
10. Wiegl, E. et. and Med. Klin.1975; 70: 664.
11. PJ Moult and S. Sherlock. Halothane-related hepatitis: A clinical study of twenty-six cases. Q J Med 1975 ;173: 99-114.
12. MJ. Cousins, JL Plummer and Hall PM. Risk factors for halothane hepatitis. Aust NZ J Surg 1989; 59:5-14.
13. WHW Inman and WW. Mushin: Jaundice after repeated exposure to halothane: An analysis of reports to the Committee on Safety of Medicines. Br M J 1984; 1:5-10.
14. LO. Warner, TJ. Beach and JP. Garvin. Halothane and children: The first quarter century. Anesth Analg 1984; 63:838-840.
15. JG. Kenna, J. Neuberger and G. Mieli-Vergani. Halothane hepatitis in children. BMJ 1987; 294:1209-1210.
16. DC. Ray and GB Drummond. Halothane hepatitis. Br J Anaesth.1991; 67:84-99.
17. F. Nomura , H. Hatano and K. Ohnishi. Effects of anticonvulsant agents on halothane – induced liver injury in human subjects and experimental animals. Hepatology 1986; 6: 952 6.
18. O. Dale and BR jr Brown. Clinical pharmacokinetics of the inhalational anaesthetics. Clinical Pharmacokinetics 1987; 12:145-167.
19. CE. Blogg. Halothane and the liver, the problem revisited and made obsolete. British Medical Journal 1986; 292:1691-1692.
20. CE. Blogg. Is halothane obsolete? Two standards of judgement. Anaesthesia 1989; 44:860-861.
21. W. Englehardt and KH. Weis. Is halothane obsolete? Two standards of judgement. Anaesthesia 1989; 44:97-100.
22. W.Englehardt and KH. Weis. Is halothane obsolete? Two standards of judgement. Anaesthesia 1989; 44:861.
23. NB.Williams. Halothane and the liver—the problem revisited. In: SE. Bennetts , ed. Proceedings of a Symposium at Bristol University Medical School, April 1986. Bristol: Bristol Royal Infirmary Publishers, 1986.
24. J. Fevery and N. Blanckaert: What can we learn from analysis of serum bilirubin. J. Hepatol 1986; 2: 113.
25. I. Gilron, B. Miline and M. Hong. Cyclooxyginase-2 inhibiters in postoperative pain management. Anesthesiology 2003;99:1198-1208 .

26. H. Wark, J. Earl and D.D. Chau. Halothane metabolism in children. Br J Anaesth. 1990;63: 474-481 .

27. JM. Murray, AS. Phillips and JP. Fee. Comparison of the effect of isoflurane and propofol on hepatic glutathione S-transferase concentration during and after prolonged anesthesia. Br J Anaesth. 1994; 72:599-601.

28. EI. Eger. Characteristics of anesthetic agents used for induction and maintenance of general anaesthesia. Am J Health Syst Pharm. 2004;15: 4: 3-10.

29. NC. Teoh and GC Farrell. Hepatotoxicity associated with non-steroidal anti-inflammatory drugs. Cli Liver Dis.2003; 7:401-13.

30. Zaleski, Linda, MD; Abello: Desflurane versus isoflurane in patients with chronic hepatic and renal disease. Anesth Analg 1993; 76:353-6.

31. Wafaa A. Fleifel. Liver and Kidney Function Tests in Patients Undergoing Surgical Operations: Potential Effect of General Anaesthesia and Peri-Operative Drug Administration. M.Sc. Thesis, University of Basrah, Medicine College, July 2005.

تأثير التخدير بالهالوثين على المرضى المصابين بأضطراب في وظائف الكبد

الخلاصة:

خلال الفترة من اذارالى كانون الأول 2006 اجريت الدراسة في مستشفى البصرة العام. على 45 مريض مصاب باعتلال وظائف الكبد تتراوح اعمارهم (6- 75) سنه، (21) 46.8% منهم ذكور ، و (24) 53.2 % أناثا ، أجريت الدراسه بصورة عشوائية لغرض تقدير السلامه وتقيم النتائج المختبريه.

هؤلاء المرضى تعرضوا للتخدير العام (الاستعمال الشائع للهالوثين المعروف بتسببه في سمية الكبد) أخذت خمسة ملليلترات من الدم الوريدي قبل وبعد العملية، ومن ثم في اليوم الأول واليوم الثالث بعد العملية – وأختبر لتحديد مستويات الانزيمات الناقله لمجموعة الامين في مصل الدم ، والفوسفاتيزالقاعدي والبليروبين الكلي وبأستعمال العدد الخاصة.

كرر اثنان وعشرون (48.89%) من المرضى التعرض للهالوثين بأجراء عمليات جراحيه مسبقه ، و 23 (51.11%) أجروا عملية جراحية واحده . وكان التغيير المعتمد في بعض المعالم مثل الانزيمات الناقله لمجموعة الامين في مصل الدم بالأضافة الى فوسفاتيزالقاعدي والبليروبين الكلي في مصل الدم .

لا تغير معتمد يلاحظ بالنسبه لجنس المرضى، ولم يظهر أي من المرضى تغيرات شديده في أي نوع من هذه المعالم عند تحليلها كلا على حده (أكثر من ثلاث مرات الحد الأعلى للقيم الطبيعيه لكل معلم) . نستنتج بذلك ان القيم المختبريه بعد العملية الجراحيه مباشرة وعلى مدى ثلاثة ايام لم تظهر أي أتجاه نحو اختلال كبير في وظائف الكبد المصابه.

الكلمات المفتاحيه :التخدير بالهالوثين، وظائف الكبد ، أختبارات الوظائف المضطربه .