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Original Article

Effect of Halothane on Liver enzymes after General Anaesthesia

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ABSTRACT

Aim: The aim of this study was to investigate the acute effects of halothane administration on postoperative liver function tests in elective surgical patient requiring general anaesthesia at our institution. Methods: Sixty patients scheduled for elective surgeries under general anaesthesia were enrolled using convenience sampling method. The patients had no history of recent alcohol intake or general anaesthesia in the previous 6 months. There was no hepatic, cardiac or renal disease. Anaesthesia was maintained within 0.75% - 1.5% halothane in 100% oxygen. Three different blood samples were collected from each patient before anaesthesia, 24 hours and 48 hours post-surgery. The plasma level of total bilirubin (TBil), albumin (Alb) and total protein (Tpro) as well as plasma activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma glutamyltransferase (GGT) were determined. Analysis of variance (ANOVA) was used to compare the differences in the mean levels of the three groups of blood samples followed by a post-hoc test using the least significant difference (LSD) method for significant ANOVA results. P-values less than 0.05 were considered statistically significant.Results: The age range of the patients who were scheduled for elective surgical procedures was between 41 and 72 years. Significant elevations were observed in AST and ALT at 24 (33.27±0.52, 34±0.49) and 48 hours (39.73±0.49, 41.28±0.48) post anaesthesia compared to pre-anaesthesia values (27.2±0.52, 29.93±0.52). There were no significant changes in either the activities of GGT and ALP, or Tbil, Alb and Tpro. Conclusion: Halothane and/or its metabolites could cause a mild increase in liver enzymes suggestive of sub-clinical liver cell alteration which buttresses the fact that halothane anaesthesia is still a safe agent in patients without pre-existing liver disease.

1. Introduction

Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane), a halogenated hydrocarbon, is an inhalational anaesthetic agent that has been widely used as an induction and maintenance volatile anaesthetic since introduced into clinical practice in 1957 [1, 2, 3]. It is well established that halothane is extensively metabolized in the liver as a lipophilic xenobiotic to hepatotoxic intermediates by monoxygenases through the cytochrome p450 system [2, 4]. Many reports of hepatotoxicity associated with halothane administration have been published and according to these reports, two types of halothane-induced hepatotoxicity namely mild and severe hepatitis were described based on the severity of symptoms [5].

The incidence of severe hepatic necrosis following halothane anaesthesia has been reported as one in every 6,000 to 35,000 patients and is fatal in 75% of these patients [6]. This association between hepatic necrosis and halothane anaesthesia or a perceived threat of litigation in relation to hepatic damage may be responsible for the decline in use of this anaesthetic for patients in many parts of the world [7]. But others have challenged this view, arguing that most cases of halothane-associated hepatitis are benign and fulminant hepatic failure is extremely rare [8].

All the arguments notwithstanding, halothane anaesthesia, has been reported to be possibly the most commonly used inhalational anaesthetic in many developing countries [9]. Despite its decade of use in anaesthetic practice at our institution in Nigeria, halothane hepatitis is rarely reported and its effect on the liver enzymes among our patients has not been previously

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documented. This study therefore, provided a good opportunity to investigate and compare the acute effect of halothane on postoperative liver functions in elective surgeries requiring general anaesthesia in our local patients.

2. Materials and Methods

After approval from the hospital research committee and written informed consent from patients, a convenient sample of 60 American Society of Anaesthesiologists (ASA) Grade 1 or 11 patients, aged between 41-72 years booked for elective surgery in the main operating suite of University College Hospital, Ibadan were enrolled in the study. Inclusion criteria included adult patients for elective surgical procedures under general anaesthesia for which halothane inhalational agent would be used, patients with no history of recent heavy alcohol intake, or general anaesthetic in the previous 6 months. The surgical procedures varied from neurosurgical procedure to elective caesarean section. The exclusion criteria included patients with unstable haemodynamic necessitating blood transfusion and patients with hepatic, renal or heart disease. Also excluded were obese and diabetic patients.

Anaesthesia Induction

After a thorough preoperative assessment, oral diazepam (5 or 10 mg) was prescribed as premedication to be administered the day before surgery for some patients while others due to surgical diagnosis had no premedication. On the day of surgery, patients were transferred to the main operating theatre suite and baseline vital signs obtained with automatic multi-parameter monitor {Dash 4000® Multi-parameter monitor (New York, USA)}. Anaesthesia induction was done with intravenous morphine 0.1 mg/kg and sodium thiopental 4 mg/kg; muscle relaxation was achieved with atracurium 0.6 mg/kg. Following adequate muscle relaxation and intermittent positive pressure ventilation (IPPV), endotracheal intubation was performed and correct placement confirmed. Anaesthesia was maintained with 0.75 – 1.5% halothane in 100% oxygen due to unavailability of nitrous oxide and IPPV was ensured throughout the surgery using the mechanical ventilator on the Drager Fabius anaesthetic machine (Draeger Medical UK Ltd). Vital signs including heart rate, non-invasive blood pressure, electrocardiogram (ECG) and arterial oxygen saturation were monitored throughout the period of surgery and anaesthesia.

Laboratory Analysis

After an average preoperative fasting of 6 -12 hours, venous blood samples (5 ml) were taken by a sterile disposable syringe then collected in plain plastic tubes at the following time intervals; immediately before anaesthesia induction (control) and 24 and 48 hours post operation (study). The serum was separated immediately after withdrawal and stored in refrigerator at -20oC until analyzed, and was investigated for estimation of serum levels of aspartate amino transferase, alanine transferase, alanine phosphatase, gamma glutamyl transferase, total bilirubin, albumin and total protein. The analyses were performed in duplicate using Hitachi 902 Automatic analyser by Boehringer Mannhein, Germany.

Statistical Analysis

All statistical analysis was performed using statistical package for social sciences (SPSS) software version 15.0. All values are expressed as mean and standard deviation (mean± SD).

The pre-anaesthetic level of enzyme was compared with that of 24 and 48 hours using one way analysis of variance (ANOVA).

A post-hoc test was done using the least significant difference (LSD) method for significant ANOVA results. A $p < 0.05$ was considered statistically significant.

3. Results

The demographic characteristics show that 60 age and sex matched patients within the range of 41 -72 years and Body Mass Index (BMI) mean±SD of 25.8 ± 2.5 were studied (Table 1).

Table 1: Patients' characteristics [number (n), mean± SD]

Parameter	Value
Sex (Male/Female)	30/30
Age (years)	54.67±1.27
Height (cm)	170±9.3
Weight (kg)	68.96±3.62
*BMI (kgm^{-2})	25.8±2.5

***Body mass index (BMI)**

Aspartate Aminotransferase (AST) (IU/I)

The mean plasma AST (I.U/L) level 24 hours after anaesthesia was 33.27 ± 0.52, significantly ($p < 0.05$) higher than pre-anaesthesia level (27.22 ± 0.52) but significantly lower than 48 hours after anaesthesia level (39.73 ± 0.49). The mean plasma AST in 48 hours after anaesthesia was also significantly ($p < 0.05$) higher than pre-anaesthesia level (Table 2).

Table 2: Mean levels of serum AST, ALT, GGT and ALP Pre-anaesthesia, 24 and 48 hours post anaesthesia in elective surgery.

Liver enzymes	Pre-anaesthesia (controls) N = 60	24 hours post anaesthesia N = 60	48 hours post anaesthesia N = 60	F-value	P- value
AST (IU/I)	27.22±0.52	33.27±0.52[a,b]	39.73±0.49[a]	142.519	0.000*
ALT (IU/I)	29.93±0.52	34.00±0.49[a,b]	41.28±0.48[a]	131.635	0.000*
GGT (IU/I)	32.27±0.75	33.36±0.72	33.62±0.72	5.267	0.406
ALP (IU/I)	83.77±2.91	86.35±2.90	88.73±2.88	0.735	0.481

* Significant at p < 0.05 (2-tailed)
a Value significantly different (p< 0.05) from group 1 value
value significantly different (p< 0.05) from group 3 value
GGT: gamma glutamyltransferase, AST: aspartate aminotransferase,
ALT: alanine aminotransferase. ALP: alkaline phosphatase

Albumin (g/L)

The mean plasma levels of albumin (g/l) 24 hours after anaesthesia (41.15 ± 0.38) was neither significantly different (p > 0.05) from the pre-anaesthesia level (41.03 ± 0.42) nor significantly different from the level at 48 hours after anaesthesia (40.35 ± 0.37) (p > 0.05, Table 3).

Total Protein (g/L)

The mean plasma total protein (g/l) level 24 hours after anaesthesia was 71.32 ± 0.38 neither significantly different (p > 0.05) from the pre-anaesthetic level (71.05 ± 0.45) nor significantly different from the level at 48 hours after anaesthesia (72.23 ± 0.37) (p > 0.05, Table 3).

Table 3: Mean levels of serum Albumin, Total Protein and Total Bilirubin Pre-operative, 24 and 48 hours post anaesthesia in elective surgery.

Parameters	Pre-anaesthesia (controls) n=60	24 hours post anaesthesia N = 60	48 hours post anaesthesia N = 60	F-value	P- value
Total bilirubin (µmol/dl)	11.80±0.23	12.36±0.22	12.55±0.19	38.943	0.073
Albumin (g/l)	41.03±0.42	41.15±0.38	40.35±0.37	1.226	0.296
Total protein (g/l)	71.05±0.45	71.32±0.38	72.23±0.37	2.403	0.093

* Significant at p < 0.05 (2-tailed)
a Value significantly different (p< 0.05) from group 1 value
value significantly different (p< 0.05) from group 3 value

4. Discussion

Liver function tests are groups of clinical biochemistry laboratory blood assays designed to give information about the state of an individual's liver. Some of these tests are associated with synthetic functionality (e.g., albumin); cellular integrity (e.g., transaminase) and conditions linked to the biliary tract (gamma-glutamyl transferase and alkaline phosphatase) [10]. Injury to the liver, whether acute or chronic, eventually results in an increase in serum concentrations of liver enzymes which usually includes plasma or serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gammaglutamyl transferase (GGT) and alkaline phosphatase (ALP) activities [4,8]. Abnormal liver enzyme levels may be a signal of liver damage or alteration in bile flow [4]. In this study, four liver enzymes: AST, ALT, GGT and ALP were chosen specifically as indices of hepatic function as well as albumin, total protein and total bilirubin levels. The mean levels of all constituents under study were within normal body range.

Routine chemistry liver function panels usually consist of AST and ALT [4]. The magnitude of amino transferases (AST and ALT) alteration can be classified as "mild" (< 5 times upper reference limit), "moderate" (5 – 10 times the upper reference limit) or "marked" (> 10 times the upper reference limit) [11]. The normal level of these liver enzymes is up to 40 I.UL-1 [12]. In this study, although the serum activities of AST and ALT were within the normal range in the patients, our data showed a significant

continuous increase in activity in AST and ALT in the patients after the elective surgery. This is in agreement with the findings of Nasiri et al [4], Elliott et al [13] and Kashifard et al [14]] which showed significant increases in activity of serum transferases after halothane induction although the changes in liver enzymes AST and ALT in their studies were statically significant, it was also within the reference range.

Several workers have came to the conclusion that high levels of GGT and ALP could be possible sign of blockage of the bile ducts, or of possible injury to, or inflammation of, the bile ducts but there were no significant differences in GGT and ALP observed in our study and their activities were still within the normal range. There was no significant change in serum total bilirubin level and this is in agreement with the findings of Gil et al [15]. Halothane has been reported to exert differential inhibitory effects on the synthesis of albumin and total proteins [15]. In this study, there was no significant drop in serum albumin and total proteins after halothane administration. Some studies have reported decreases in total proteins after halothane [7, 16] but others observed no change in total protein concentration [17].

Most reported cases have linked halothane administration to hepatotoxicity in patients [2, 4, 5]. Halothane-induced hepatotoxicity has been reported to be the consequence of both oxidative and reductive microsomal cytochrome P450 enzyme induction, and lipid peroxidation which results in denaturation of cell membrane phospholipids [5]. These processes cause changes in membrane's biochemistry of liver cells which could manifest as a minor hepatic dysfunction associated with a transient rise in serum transaminases [6].

It is important to note that in spite of varying duration of subjects exposure to halothane anaesthesia, there was no singular enzyme elevation beyond the normal reference interval which buttresses the fact that halothane anaesthesia is still a safe agent in patients without preexisting liver disease and 'halothane hepatitis' is uncommon. We suggest use of alternative inhalational agents such as enflurane, isoflurane, sevoflurane, and desflurane which although more expensive than halothane [18, 19], undergoes minimal metabolism when compared with halothane [20] for patients at risk of halothane hepatitis such as in repeat surgeries, obese patients and patients with liver disease [21, 22].

5. Conclusion:

The results from this study showed that halothane or its metabolites, or both, could cause a mild increase in liver enzymes thereby, providing further evidence that a short exposure to halothane could cause direct but subclinical liver cell alteration.

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