

The Effect of Occupational Exposure to Wasted Halothane on Liver Functions of Operating Room Personnel

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Abstract

The aims of our study were to determine concentrations of wasted halothane in operating rooms and to investigate the effect of halothane pollution on liver functions of exposed personnel. The studied group included operating room personnel from the clinic of surgery, Novi Sad University Clinical Center. Surgeons were exposed to an average concentration of 29.41 mg/m³, anesthesiologists to 34.60 mg/m³, instrumenting nurses to 28.62 mg/m³ and anesthetists to 30.09 mg/m³ of halothane. Anesthesiologists in 32% of operations were exposed to a concentration higher than the threshold limit value, surgeons in 23%, instrumenting nurses in 22% and anesthetists in 18% of operations. Laboratory values of the liver function indicators in the exposed group were significantly worse than in the control group. The results suggest that exposure to wasted halothane may be harmful to the livers of operating room personnel.

Keywords: air pollutants, halothane, occupational exposure, operating room personnel, liver

Introduction

Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane), a halogenated hydrocarbon, is inhalational anesthetic. About 80% of inhaled halothane is exhaled, and about 20% is metabolized, mostly in the liver, to its final metabolites – trifluoro-acetic-acid (CF₃COOH) and bromine (Br⁻) – which are eliminated by urine [1].

Halothane was introduced into clinical use in 1956. Soon after, it was reported that halothane damages liver parenchyma [2-4].

Liver damage is the consequence of microsomal cytochrome P450 enzyme induction, and lipid peroxidation which results in denaturation of cell membrane phospholipides [5-9]. These processes cause changes in a membrane's biochemistry of liver cells [10, 11].

The current theory is that oxidative metabolism of halothane produces a trifluoroacetyl (TFA) halide. This compound changes the structure of cytochrome P450 and other proteins, converting them into haptens, resulting in a dramatic inflammatory response in the liver in susceptible individuals. The presence in the plasma of anti TFA antibodies is common in patients with halothane hepatitis, but not other forms of hepatitis. Minor hepatic dysfunction associated with a transient rise in transaminases is more common and may be associated with the direct hepatotoxic effect of reductive metabolites. Autoregulation of the hepatic arterial bed is severely impaired by halothane [12].

These metabolic and chemical processes are affected by many factors, including age, disease, drug interactions and, perhaps most importantly, genetics [13].

Halothane hepatotoxicity is not restricted to patients undergoing anesthesia. Liver damage following occupational exposure to halothane has been reported in medical personnel, including anaesthetists and surgeons [14].

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There is continuing debate concerning the possible deleterious effects of occupational exposure of operating theatre personnel to inhalational anesthetics [12].

Trace concentrations of waste anesthetic gases have been implicated as a cause of various adverse health effects in operating room personnel [15].

Data on occupational exposure to inhaled anesthetics in Eastern European operating room personnel are rare [16].

We determined the concentration of waste halothane in operating rooms and examined the influence of halothane concentrations on the liver functions of exposed operating room personnel.

Material and Methods

Subjects and Materials

We studied operating room personnel in the Clinic of Surgery, University Clinical Center of Novi Sad, Serbia, who were exposed to halothane in a working environment.

All clinic operating room personnel were called to a preventive-periodical health examination (N=237). A total of 27 medical workers did not respond to examination: 12 surgeons, 9 instrument nurses and 1 anesthetist.

The control group consisted of administrative personnel of a bank in the city of Novi Sad (N=74), who were not exposed to chemical compounds or heavy workloads at their workplaces. A total of four administrative personnel from the Bank did not respond to examination.

Both groups of workers received medical checkups in the Institute of Occupational Health Novi Sad in accordance to legislation on preventative examinations of workers [17].

The examination, done by the same researcher, included detailed personal (sex, age) and medical history, clinical examination and calculation of body mass index (BMI). The laboratory tests of liver function parameters included: serum bilirubines, alkaline phosphatase (AP), gamma glutamil transpeptidase (γ GT), (for biliary retention syndrome), asparthat transaminase (AST), alanin transaminase (ALT), lactat dehidrogenase (LDH) (for hepatic cell necrosis syndrome) and, finally, pseudo-cholinesterase activity (PsH) and concentration of plasma proteins – total, albumin and globulins (α_1 , α_2 , β , γ) (for hepatic cell insufficiency syndrome) [18].

On the basis of data obtained, due to differences in a diet in rural and urban residents [19-21], we excluded from both groups those subjects who lived outside the city of Novi Sad and persons with a vegetarian diet.

Also, we excluded from both groups subjects who daily consumed alcohol containing more than 40 g (for men) or 20 g (for women) of pure ethanol, those who in a period of 15 days before the examination took medications and those who were carriers of hepatitis B antigen or with Gilbert syndrome.

The studied group of 191 (80.6%) of all exposed operating room personnel (N=237) was formed. The group

included 4 subgroups according to the workplace (surgeons, anesthesiologists, instrumenting nurses, anesthetists). The subgroups included 81 (76.4%) of all exposed surgeons (N=106), 37 (100%) anesthesiologists, 48 (73.8%) of all exposed instrumenting nurses (N=65), and 25 (86.2%) of all exposed anesthetists (N=29).

Control group included 64 (86.5%) of all administrative workers (N=74) of the bank.

Analytical Methods

Sampling of air in surgical theaters was carried out five times for every workplace, which means that in every observed surgical theater 20 samples were taken. In 12 theaters a total of 240 samples were taken. "Average concentration" is the average concentration of halothane from 20 samples at each theater.

Air samples were taken using the individual sample principle, which means that air was taken in the subject's breathing zone by a rubber tube, attached at the shoulder of surgical clothes, with the tube opening at 10-15 cm from mouth and nose.

Air sampling began 10-15 min after the initial phase of surgery, i.e. 20-30 min. after the administration of anesthetics.

The sampling method consisted of filtration of 6 L of air, with air flow of 0.2 L/min. Collectors were 10-cm-long glass tubes containing 150 mg of active coal. Sample analyses were done by halothane desorption from active coal using n-hexane. Halothane evaporations were determined by gas chromatography on a Hewlett-Packard gas chromatograph, 6890 series (Hewlett-Packard Company, Wilmington, DE, USA). Analyzed conditions were as follows: column "HP-5" (30 m x 0.32 mm internal diameter, 0.25 μ m film), temperature 35°C (2.5 min), 50°C/min to 270°C. Carrier: helium, 70 cm/s (constant flow). Detector: ECD (electron-capture-detector), 300°C. Injected volume: 1 μ L, split 100:1, 270°C. Under these conditions, retention time for halothane was 0.97 minutes, and the lower limit value for halothane detection was 0.01 mg/m³ [22].

According to the Serbian legislation the threshold limit value (TLV) for halothane is 40 mg/m³ (4.9 parts per million (ppm)) [23].

Statistical Approach

Statistical analyses included calculation of centile distribution, central tendency measures (mean value, standard deviation (\pm SD) and coefficient of variation (CV)) analysis and Student's t-test.

Results

There were no statistically significant differences in age, sex and BMI between the studied and control groups. However, in subgroups there were significant differences in age between medical doctors (surgeons –

Table 1. Liver function parameters in operating room personnel and the control group.

Liver function parameters	Operating room personnel (N=191)		Control group (N=64)		t-test
	mean± SD*	CV** %	mean± SD	CV %	
Total bilirubine (µmol/l)	12.10±5.27	43.5	9.77±2.90	29.7	p<0.001
Direct bilirubine (µmol/l)	1.78±1.17	65.7	1.74±0.78	44.6	NS***
Indirect bilirubine (µmol/l)	10.32±4.86	47.1	8.03±2.30	28.6	p<0.001
AP (U/l)	58.69±13.73	23.4	49.53±13.57	27.4	p<0.001
γGT (U/l)	20.73±12.74	61.5	14.88±6.99	46.9	p<0.001
AST (U/l)	15.64±6.42	41.1	11.89±4.78	40.2	p<0.001
ALT (U/l)	18.30±8.20	44.8	14.09±7.38	52.4	p<0.001
LDH (U/l)	87.81±19.97	22.7	69.13±15.40	22.3	p<0.001
PsH (ΔpH/30'/mL)	1.70±0.22	12.7	1.85±0.13	6.9	p<0.001
Total proteins (g/L)	68.82±4.34	6.3	66.80±3.79	5.7	p<0.001
Albumin (g/L)	39.88±4.55	11.4	40.90±3.22	7.8	NS
A/G index	1.43±0.27	19.2	1.63±0.27	16.6	p<0.001
α ₁ –globulins	0.046±0.008	18.2	0.045±0.008	19.7	NS
α ₂ –globulins	0.075±0.016	21.7	0.074±0.012	17.1	NS
β-globulins	0.11±0.02	16.3	0.10±0.018	17.4	NS
γ-globulins	0.18±0.02	15.1	0.15±0.029	18.5	p<0.001

*SD – Standard deviation

**CV – Coefficient of variation

***NS – Not significant

44.6±10.4 years, anesthesiologists – 43.2±9.3 years) and members of the surgical team with vocational school training (instrumenting nurses – 33.9±8.4 years; anesthesiologists – 33.0±6.2 years), p<0.01.

Also, the BMI of surgeons (26.57±3.18) was significantly higher compared to other subgroups (anesthesiologists – 24.57±3.37, instrumenting nurses – 23.99±3.38, and anesthesiologists – 24.88±3.03), (p<0.01, p<0.0001 and p<0.05, respectively).

Results of Ambient Monitoring of Wasted Halothane

In all operating rooms a passive waste gas scavenging system was installed. The air conditioning devices were not used. The operating rooms have no forced ventilation.

It was found that the average concentration of wasted halothane vapours to which the examined operating room personnel were exposed to was 30.67 mg/m³.

Concerning the members of the surgical team, it was found that surgeons were exposed to an average concentration of 29.41 mg/m³ of halothane, anesthesiologists to 34.60 mg/m³, instrumenting nurses to 28.62 mg/m³ and anesthesiologists to 30.09 mg/m³ of halothane.

Statistical testing (analysis of variance, between groups and within groups, F = 0.325, p>0.807) shows that there

were no significant differences between average concentrations of halothane among tested surgical theaters that members of surgical teams were exposed to, i.e. that all profiles within the surgical team were working in approximately similar conditions regarding exposure to waste halothane.

Although members of the surgical team were exposed to approximately similar average concentrations of halothane, by computation of centile distribution regarding TLV, it was found that anesthesiologists in 32% (C₆₈) of operational procedures were exposed to halothane concentrations above TLV, surgeons in 23% (C₇₇), instrumenting nurses in 22% (C₇₈) and anesthesiologists in 18% (C₈₂) of operational procedures.

Results of Liver Function Parameters

The liver function parameters were determined in 191 operating room personnel exposed to halothane vapors, and in the control group (Table 1).

Average values of “biliary retention syndrome” (apart from direct bilirubine – p>0.814) and “hepatic cell necrosis syndrome” parameters in operating room personnel were significantly higher (p<0.001 for all) than in control group. Pseudocholinesterase activity in exposed medical personnel was significantly lower (p<0.001), while average value of total proteins was significantly higher (p<0.001) than in control group (Table 1).

Table 2. Liver function parameters in 4 subgroups formed according to the workplace (surgeons, anesthesiologists, instrumenting nurses, anesthetists).

Liver function parameters	Surgeons (N=81)		Anesthesiologists (N=37)		Instrumenting nurses (N=48)		Anesthetists (N=25)	
	mean± SD*	CV** %	mean± SD	CV %	mean± SD	CV %	mean± SD	CV %
Total bilirubine (µmol/L)	13.00±6.10	46.9	11.53±3.43	29.8	11.15±5.02	45.0	11.84±4.55	38.4
Direct bilirubine (µmol/L)	1.77±1.34	76.1	1.86±1.12	60.3	1.67±0.94	56.6	1.90±0.96	50.6
Indirect bilirubine (µmol/L)	11.24±5.59	49.7	9.68±3.20	33.0	9.48±4.69	49.4	9.94±4.16	41.7
AP (U/L)	60.35±13.69	22.7	56.43±13.69	24.3	57.19±14.84	25.9	59.52±10.58	17.7
γGT (U/L)	26.60±15.86	59.6	17.00±7.00	41.2	15.79±7.51	47.5	16.72±7.03	42.1
AST (U/L)	17.44±6.78	38.8	13.84±8.28	59.8	14.27±3.87	27.1	15.08±4.14	27.4
ALT (U/L)	21.07±8.76	41.5	16.08±9.27	57.6	15.56±4.40	28.2	17.84±7.40	41.4
LDH (U/L)	91.02±22.27	24.5	89.00±15.98	17.9	84.27±19.24	22.8	82.40±16.21	19.6
PsH (ΔpH/30'/mL)	1.72±0.24	14.1	1.72±0.20	11.7	1.66±0.15	8.8	1.71±0.25	14.8
Total proteins (g/L)	69.25±4.47	6.5	68.73±4.42	6.4	68.58±3.99	5.8	68.04±4.28	6.3
Albumin (g/L)	39.7±4.65	11.7	40.93±4.49	10.9	39.75±4.41	11.1	39.18±4.31	11.0
A/G index	1.39±0.25	18.4	1.53±0.31	20.1	1.43±0.27	18.9	1.40±0.25	18.0
α ₁ -globulins	0.047±0.009	18.9	0.044±0.007	17.0	0.045±0.006	14.6	0.047±0.01	21.2
α ₂ -globulins	0.079±0.02	21.2	0.069±0.01	19.8	0.075±0.01	23.2	0.075±0.01	19.5
β-globulins	0.11±0.02	15.3	0.10±0.02	15.5	0.10±0.018	17.1	0.11±0.01	16.2
γ-globulins	0.18±0.03	14.6	0.18±0.03	17.5	0.18±0.02	13.8	0.18±0.02	15.3

*SD – Standard deviation

**CV – Coefficient of variation

The liver function parameters in 4 subgroups formed according to the workplace (surgeons, anesthesiologists, instrumenting nurses, anesthetists) are presented in Table 2.

Statistical analysis has shown that surgeons have significantly higher activities of γGT, AST and ALT compared to anesthesiologists and instrumenting nurses, and only γGT compared to anesthetists.

Discussion of Results

Average concentration of waste halothane detected in examined surgical theaters has remained under TLV for halothane of 40 mg/m³ (4.9 ppm). Occupational exposure to halothane was assessed in hospital operating theaters in Poland, too (Łódź and its satellite towns). Also, the concentrations of halothane were lower and did not exceed the respective Polish TLV (40 mg/m³) in the majority of the studied hospitals [24].

Statistical analysis showed that all profiles within a surgical team were engaged in approximately similar conditions regarding exposure to “wasted” halothane. Although members of a given surgical team were exposed to approx-

imately similar average concentrations of halothane, anesthesiologists were more endangered than other members of the surgical team because they were more frequent than others exposed to halothane concentrations above TLV. Halothane has quite low TLV, ranging from 0.5 ppm (Australia) to 5 ppm (Sweden and Germany). The National Institute for Occupational Safety and Health (NIOSH) has established a recommended exposure limit (REL) of 2 ppm (16.2 mg/m³) for halothane (as a waste anesthetic gas) as a 60-minute ceiling limit that should not be exceeded during any part of the workday. The American Conference of Governmental Industrial Hygienists (ACGIH) has assigned halothane a TLV of 50 ppm (404 mg/m³) as a time-weighted average (TWA) for a normal 8-hour workday and a 40-hour workweek [25-27].

In last few years the use of halothane has been less extensive in Serbian hospitals. However, it varies between different areas of the country. The use is less extensive in more developed areas, like ours.

Efforts should be made to obtain funds to replace the current anesthesia machines with modern ones equipped with evaporators suitable for anesthetics like enflurane, desflurane, sevoflurane etc. Moreover, a change from inhalation

to intravenous anesthesia is strongly recommended whenever it is possible. Active scavenging of waste anesthetic gases is recommended for areas to reduce contamination [15, 28].

Some authors have considered that maximum reduction of waste gases is best achieved by having a proper non-recirculating air-conditioning system (with a minimum of 20 air changes/hour), a save system, which includes the collection of waste gases from the equipment and their removal outside, and by using low flows of anesthetic gases. Filling the vaporizers should be done through closed attachments and, if possible, after the working hour; spillage of volatile agents must be avoided [29].

It is recognized that each anesthetist develops a personal technique when carrying out a procedure. However, some simple measures to reduce pollution were identified, such as turning off the gas flow during intubation, and ensuring that gases are turned off before transferring the patient into the theatre [30].

Operating room personnel had significantly higher average concentrations of indirect and total bilirubine, while there were no statistically significant differences in concentrations of direct bilirubine between these groups.

Bruce DL. described an increase of erythrocyte cell membrane resistance to rupture in persons exposed to halothane, which means decreased production of indirect bilirubine by erythrocyte breakdown [3]. On the other hand, Grundmann U., et al. assumed that increased concentrations of indirect bilirubine in peripheral blood of exposed medical personnel could be a result of lowered liver perfusion in persons exposed to halothane, provoking disturbance in glucuroconjugation of indirect bilirubine [5].

Also the activity of alkaline phosphatase was significantly higher, which could be caused by the above-mentioned disturbed glucuroconjugation of indirect bilirubine and consequently decreased alkaline phosphatase separation in bile on the biliary pole of hepatic cells [13].

Significantly higher activity of γ GT found in medical personnel could result from an increased number of damaged and destroyed epithelial cells of bile ducts, due to lowered liver perfusion [6], and its exposure to aggressive free radicals generated during halothane metabolism [7].

Analyses showing the status of hepatic cell membrane (AST, ALT, LDH) revealed that average concentrations of all three parameters were significantly higher in the exposed medical personnel than in the control group. Activities of these enzymes, however, pointed to only mild liver function disturbance, manifested as an increase of hepatic cell membrane permeability and only a lower number of additionally destroyed hepatic cells than usual.

From the group of "hepatic cell insufficiency syndrome" parameters, average blood concentration of pseudo-cholinesterase in the exposed medical personnel was significantly lower than in the bank personnel, which points to a disturbance in synthetic functions of hepatic cells in medical personnel.

Protein electrophoresis (especially albumin-globulins index - A/G) has shown that albumin fraction in medical personnel was decreased regarding to the control group,

and globulins fraction was increased, especially the γ -globuline fraction, which explains finding a significantly higher concentration of total proteins in the medical personnel.

Having in mind that halothane may contribute to liver function disturbance in exposed medical personnel, we were interested in whether impairment is connected to workplace within a surgical team.

Considering a similar exposure to halothane, the reason for significantly higher values of liver function tests (γ GT, AST and ALT) in the surgeons was not clear.

The surgeons were significantly older compared to instrumenting nurses and anesthetists. Average age of surgeons was about 44 yr. It was reported that 70% of halothane-induced hepatic dysfunctions occur in patients older than 40 yr, and the peak incidence occurs between 50 and 60 yr [31]. However, significant age difference was noticed in anesthesiologists (43 yr) compared to instrumenting nurses and anesthetists, and no significant difference in liver functions was found between these groups.

Also, it seems that these findings could be explained by significantly higher BMI in surgeons compared to the other subgroups of operating room personnel. Hepatic dysfunction is more common in obese than in non-obese patients. 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, which might further predispose them to liver injury [32].

Finally, it is possible that non occupational agents (excessive coffee consumption, denied alcohol drinking, etc), could additionally increase liver tissue hypoxia or activate cytochrome P450 2E1 enzyme [33, 34].

Therefore, significant change of liver function parameters in surgeons compared to their co-workers could be attributed to factors outside the workplace mentioned above.

Regular monitoring of air quality should be routine. The situation with regard to air quality in operating rooms is complicated because gaseous pollution consists not only of waste anesthetic gases but also the propellants from different sprays, vapours from scrubbing and cleansing agents and possibly other volatile or gaseous products [35].

Shortcomings of the field studies of occupational exposure to halothane and other anaesthetic agents are related to the absence of reliable markers of health effects from exposure to low-doses of anaesthetics and the difficulties of deconstructing the combined effect of low-doses of chemicals and exposure to various other chemical and physical factors [29].

Conclusions

In summary, our study revealed that average concentration of wasted halothane detected in examined surgical theaters has remained under TLV for halothane of 40 mg/m³, and that all members of a surgical team were engaged in approximately similar conditions regarding exposure to wasted halothane, although anesthesiologists were some-

what more endangered. The liver function disturbances were manifested as statistically significant changes in parameters of "biliary retention syndrome" (apart for direct bilirubine), "hepatic cell necrosis syndrome" and "hepatic cell insufficiency syndrome" (except for serum albumin) in the exposed medical personnel compared to the control group. The results suggest that exposure to wasted halothane may be harmful to the liver of operating room personnel. A particular position within a surgical team probably has no important influence on the level of liver function impairment. However, further research is needed to elucidate our findings because the debate on health effects of halothane is ongoing and important.

Acknowledgements

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