Retrospective Study of Post-anesthetic Mild Liver Disorder Associated with Inhalation Anesthetics, Halothane and Enflurane

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The incidence of post-anesthetic mild liver disorder (PAMLD) was compared between 928 patients administered halothane and 1,766 patients administered enflurane. They were selected from 19,504 surgical patients administered general anesthesia at Kyushu University Hospital over the past 6 years and 4 months. They had had normal liver function before operation and had no history of blood transfusion. Alanine aminotransferase (ALT) levels exceeding 70 IU·l^{-1} within 180 days after operation were found in 226 patients in the halothane group (24.4%), and in 250 patients in the enflurane group (14.2%) ($P< 0.01$). Both maximum ALT levels and duration of ALT elevation were higher and longer in the halothane group ($P< 0.01$). These results suggest that, not only in the development of fulminant hepatitis but also in PAMLD, enflurane is less hepatotoxic than halothane. (Key words: anesthetics, volatile: halothane, enflurane, liver: hepatitis, drug toxicity)

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Halothane anesthesia is currently applied to a quite limited number of the patients who undergo surgery in Kyushu University Hospital compared with enflurane anesthesia (fig. 1), mainly because anesthesiologists foresee the development of liver disorder following halothane anesthesia.

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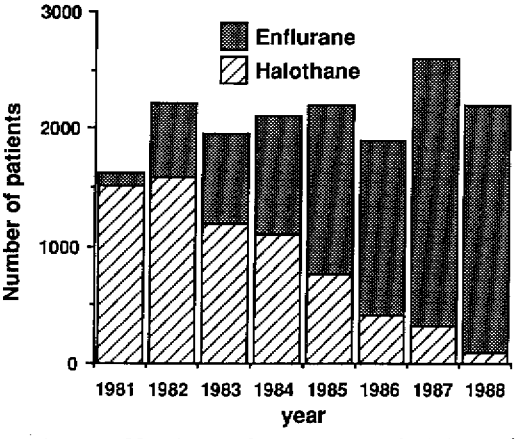

Fig. 1. Number of patients administered halothane or enflurane in the Kyushu University Hospital from 1981 to 1988.

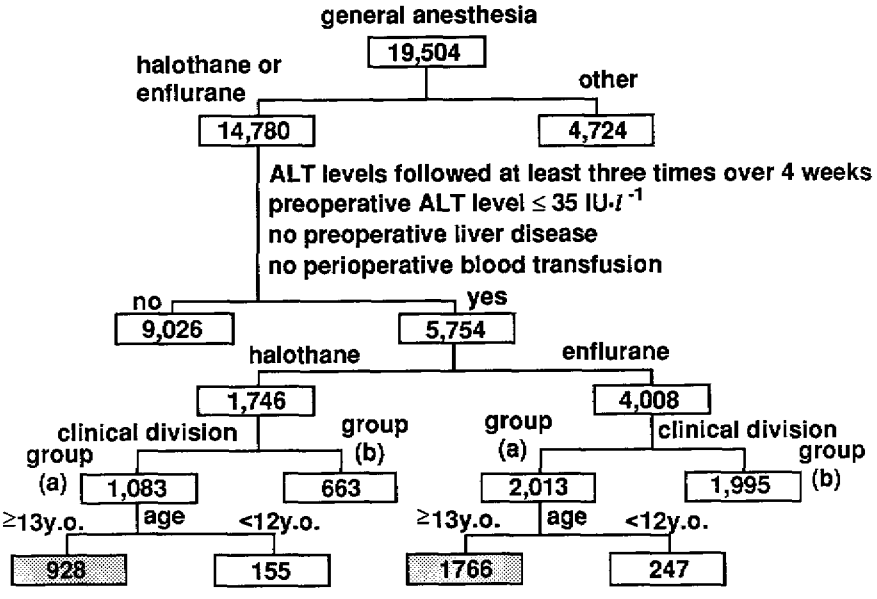

Fig. 2. Patient selection flow chart. Comparisons of the incidence and the severity of post-anaesthetic mild liver disorder (PAMLD) were studied between 928 patients in the halothane group and 1766 patients in the enflurane group. The group of department (a): General Surgery, Ophthalmology, Gynecology & Obstetrics, Orthopedic Surgery, Neurosurgery and Urology; Group (b): Oto-Rhino-Laryngology, Dermatology, Cardiac Surgery, Pediatric Surgery and other departments.

The incidence of fulminant hepatitis associated with clinical anesthesia is stated to be around 1 in every 30,000 anesthesia patients[1-7]. However, the incidence of subclinical liver disorder, which is detectable only by the elevation of serum alanine aminotransferase (ALT) activity, is not well known. There are few reports investigating the incidence of post-anesthetic mild liver disorder (PAMLD) because of difficulty in evaluating factors of hepatotoxic effect in perioperative patients. In this follow-up study of patients who had undergone surgery under general anesthesia, the incidence and severity of PAMLD after halothane anesthesia was surveyed and compared with that after enflurane anesthesia.

Patients and Methods

Patients

From June 1982 to October 1988 (6 years and 4 months), 19,504 operations were performed under general anesthesia in our institution. Through case history database of our integrated hospital information system, patients who had been administered inhalation anesthetics during operation were selected as follows (fig. 2).

1) Patients administered either halothane or enflurane.
2) Patients whose serum alanine aminotransferase (ALT) levels were measured at least three times over 4 weeks after general anesthesia
3) Patients whose ALT levels were examined at least once before operation
4) Excluded from 1), 2) and 3) were:
   a. Patients whose ALT levels were over 35 IU·l^{-1} just before the anesthesia
   b. Patients diagnosed as having liver diseases (neoplastic disease of

Table 1. Distribution of patients by department, age and sex

	Halothane group (N=928)	Enflurane group (N=1766)	P value
Department			
General Surgery	385	666	
Ophthalmology	182	333	
Gynecology & Obstetrics	133	272	NS*
Orthopedic Surgery	108	245	(p=0.319)
Neurosurgery	90	186	
Urology	30	64	
Mean age (± SD)	44.4 (± 16.7)	47.3 (± 17.7)	< 0.05**
Sex ratio (Male/Female)	0.573 (338/590)	0.880 (785/981)	< 0.01*

*chi-square test
**t test
NS: not significant; SD: standard deviation

liver, liver cirrhosis, hepatitis or bilially tract stones)

c. Patients who had received blood transfusion within 6 months before and/or 1 month after general anesthesia.

5,754 patients were selected and divided into two gropus; 1,746 (30.3%) in the halothane group and 4,008 (69.7%) in the enflurane group. The background information of the patients in these two groups was analyzed for the department, age, sex and history of administration of inhalation anesthetics. Of the 5,754 patients analyzed by department for grouping, the number of patients in the halothane and enflurane groups, respectively, were 484:482 from Pediatric Surgery, 387:668 from General surgery, 244:420 from Ophthalmology, 110:216 from Neurosurgery, 135:272 from Gynecology and Obstetrics, 160:335 from Orthopedic Surgery, 47:102 from Urology, 2:5 from Cardiac Surgery, 148:1253 from Oto-Rhino-Laryngology, 27:239 from Dermatology and 2:16 from other departments. In Oto-Rhino-Laryngology and Dermatology, the number of enflurane anesthesia cases were extremely high compared to halothane anesthesia cases. In Pediatric Surgery the number receiving halothane was higher than the number receiving enflurane. There were a little patients in Cardiac Surgery and other departments. The mean age was significantly different between the halothane (28.3 ± 23.6) and enflurane groups (38.8 ± 22.9) ($P < 0.01$). For children, halothane was used more frequently than enflurane. For these reasons, Oto-Rhino-Laryngology, Dermatology, Pediatric Surgery, Cardiac Surgery and other departments patients, and patients aged under 12 years were excluded from the comparison. Consequently, 928 patients were selected in the halothane group and 1,766 in the enflurane group. There was no significant difference of patient distribution in departments anesthetized with either halothane or enflurane. The mean age was 44.4 years in the halothane group and 47.3 years in the enflurane group. The male/female ratio of the halothane group was significantly lower than that of the enflurane group at 0.573 (338/590) to 0.880 (785/981) ($P < 0.01$) (table 1).

Follow-up of liver function

ALT levels were followed to evaluate the postoperative liver function for up to 180 days after the operation.

Table 2. Percentage of patients with ALT elevation

	Halothane group (N=928)	Enfluane group (N=1766)	P value*
Male	27.8% (94/338)	17.8% (140/785)	< 0.001
Female	22.3% (132/590)	11.2% (110/981)	< 0.001
Total	24.4% (226/928)	14.2% (250/1766)	< 0.001

*chi-square test

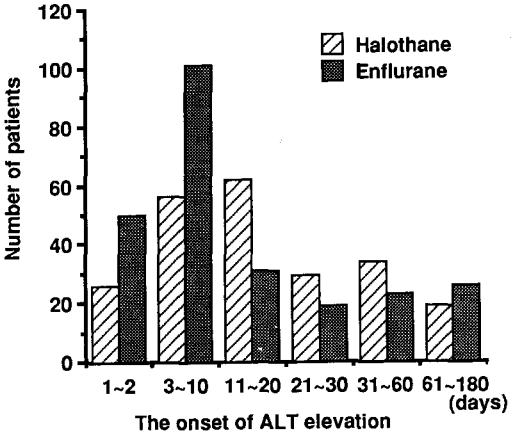

Fig. 3. The number of PAMLD patients anesthetized halothane or enflurane by the onset of alanine aminotransferase (ALT) elevation. Statistically significant difference ($P < 0.01$) between the halothane and enflurane group (Wilcoxon's rank sum test).

Patients whose ALT levels were over 70 IU·l^{-1} (twice the normal upper limit of this hospital) at least twice were defined as PAMLD cases. The onset of ALT elevation, the maximum ALT value and the duration of ALT elevation were also examined.

Statistics

The chi-squared test was used to compare distribution of the department, sex ratio and the incidence of PAMLD between the halothane and enflurane groups. The onset and duration of ALT elevation and maximum ALT values between the two groups were compared using Wilcoxon's rank sum tests respectively. Ordinary t test was used for comparison of age distribution. Computations were carried out using the statistical package, BMDP 4F, 3D, and 3S on an IBM system 4381 computer[8].

Results

The incidence of PAMLD (table 2)

In the halothane group (226 patients), the incidence of PAMLD was significantly higher than in the enflurane group (250 patients) at 24.4% to 14.2% respectively. The male vs female ratio was 94/132 (0.71) in the halothane group and 140/110 (1.27) in the enflurane group. In both sex groups, the halothane group had a significantly higher incidence of PAMLD than the enflurane group ($P < 0.001$). Of the 476 PAMLD patients, 8 patients were administered with the same anesthetics repeatedly; 4 in the halothane group and 4 in the enflurane group.

Severity of PAMLD

1) The onset of ALT elevation (fig. 3)

The onset of ALT elevation peaked between the 11th and 20th day after operation in the halothane group, while it was between the 3rd and 10th day after operation in the enflurane group. ALT values in the enflurane group were more likely elevated at an earlier stage than the halothane group ($P < 0.01$).

2) Maximum ALT values (fig. 4)

Maximum ALT values were concentrated between 100 and 199 IU·l^{-1} in both groups, 32.3% of all the

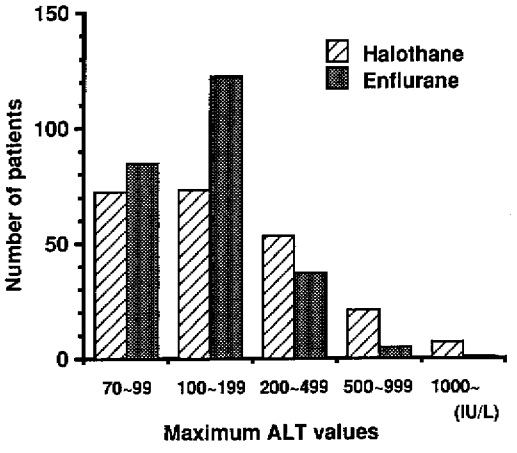

Fig. 4. The number of PAMLD patients anesthetized halothane or enflurane by the maximum ALT value. Statistically significant difference ($P < 0.01$) between the halothane and enflurane group (Wilcoxon's rank sum test).

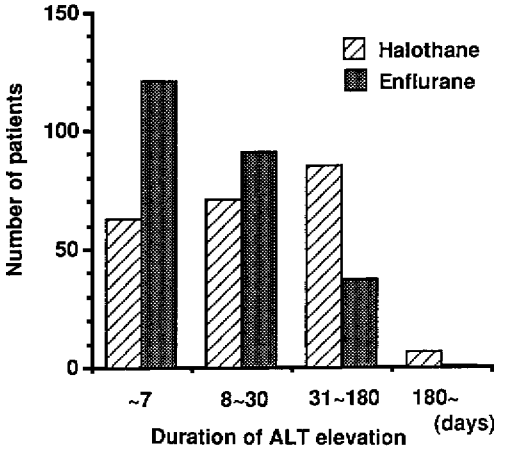

Fig. 5. The number of PAMLD patients anesthetized halothane or enflurane by the duration of ALT elevation. Statistically significant difference ($P < 0.01$) between the halothane and enflurane group (Wilcoxon's rank sum test).

halothane group patients and 48.8% of those in the enflurane group showed their maximum ALT values in the postoperative period. Of patients with maximum ALT over 200 IU·l^{-1}, there were 35.9% in the halothane group, which was larger than the 17.2% in the enflurane group ($P < 0.01$). There were 7 patients in the halothane group and 1 patient in the enflurane group over 1000 IU·l^{-1} (clinically distinguished hepatitis patients). The maximum ALT values of the halothane group were significantly higher than those of the enflurane group ($P < 0.01$).

3) Duration of ALT elevation (fig. 5)

The duration of ALT elevation of the halothane group was significantly longer than that of the enflurane group ($P < 0.01$), centered between 31 to 180 days in the halothane group (37.6%) and under 7 days in the enflurane group (48.4%).

Discussion

There have been many reports of the incidence of fulminant hepatic failure associated with inhalation anesthetics, especially with halothane. These report the incidence of fulminant hepatitis after halothane anesthesia as 1:6,000 to 1:40,000, with incidence after enflurane less than one tenth that of halothane[1-7]. However, since halothane has several merits such as ease of induction for infants and economy, its use should not be restricted if the incidence of adverse effects are clinically meaningless. On the other hand, several studies have reported that the existence of mild and transient abnormalities in liver functions after halothane anesthesia are not uncommon[9-12].

Therefore, it was necessary to determine by a large epidemiological study whether or not there are real hazards associated with halothane use. It is very complicated and almost impossible to both prospectively and retrospectively study the hazards of mild liver toxicity by halogenated anesthetics after general anesthesisa because there exist many factors, especially during the perioperative period, which are potentially hepatotoxic. The first factor is anesthesia or surgical manipulation itself, for example, hypotension,

hypoxemia, mechanical compressions. The second factor is drugs, not only inhalation anesthetics but also antineoplastic agents, antibiotics, etc. The third factor is blood transfusion. The fourth factor is infection due to bacteria or viruses after operations. Age, sex, obesity and preoperative liver dysfunction have also been considered to be influencing factors[7,13]. It is further complicated because these factors exist at the same time perioperatively.

Several attempts have been made to clarify by prospective study whether or not halothane is more likely to be associated with liver disorder than enflurane[14–18]. Fee and colleagues[16,17], compared post-anesthetic liver function of patients repeatedly anesthetized with the two anesthetic agents. They concluded that halothane seemed more often responsible for liver disorder than was enflurane. Other studies reported no significant difference of change in hepatic serum enzymes between the two anesthetics[14,15,18]. The main reason for these controversial conclusions was the difficulty of collecting enough cases for statistical analysis.

This problem was resolved by our present large scale study. Two fortunate events allowed us to find a solution to this problem. The first, unexpectedly, randomization of the two agents was made possible as a result of the delayed introduction of enflurane in Japan. Although the reason for the decision by our anesthetists at the time of operation as to which agent they would employ can not be discerned, in the first few years of our study period halothane was used exclusively and, by the later period, this was true of enflurane. For this reason, the selection bias was considered negligible. The second fortunate event was a new approach to computer assistance that became available. We feel we have succeeded in obtaining a large enough number of patients in each group for objective assessment through statistical analysis by analyzing the huge amount of accumulated data in our hospital computer without exhaustive effort. It would probably have been impossible to carry out such complicated algorithms as were necessary to use to make two groups for statistical evaluation and to except the many influencing factors other than the two inhalation anesthetics without computer assistance.

Although our present study was not done prospectively, the conclusions drawn may be reliable because there were enough remaining patients in each group after the several restrictions to prove statistically accurate. Our restrictions were made according to the findings of past studies[1,7,13]. The incidence of PAMLD associated with halothane and enflurane by the chi-squared method for simple 2×2 contingency tables showed a statistically significant difference ($P < 0.01$). Our study also revealed that PAMLD after halothane anesthesia was nearly two-fold higher than that of enflurane, and that the severity of halothane induced liver disorder was greater than that of enflurane.

Indeed, the pathogenesis of liver disorder as a result of halogenated anesthetics is unknown. Therefore, it is difficult to explain why the difference exists between the incidence of PAMLD after administration of halothane and enflurane. Two hypotheses have been long proposed. One is secondary immunological response and the other is direct toxicity of metabolized substances from these agents. Recently, Kenna and colleagues[19–24] reported the existence of anti-trifluoloacetic acid (TFA) antibodies by Western blotting in severe halothane hepatitis patients. But, the clinical course and onset time of PAMLD are different from that of the fulminant type and they didn't

find anti-TFA antibodies in the sera of symptomless patients. A secondary effect by immunological process has usually taken more than a week even if patients had already been exposed to repeated administration of these anesthetic agents. These phenomena can not explain the pathogenesis of PAMLD.

Direct toxicity of inhalation anesthetics looks likely to be related to PAMLD. The effects of administration of halothane and enflurane on splanchnic blood flow and metabolic rates are much different. Whereas 11% to 25% of halothane administered was metabolized, only 2.4% of enflurane was[25]. Metabolites and free radicals produced through both the oxidative and the reductive pathway affect the liver[26,27]. Halothane diminishes hepatic blood flow and induces hypoxia in liver tissue much more than does enflurane[28–31]. These data suggest that halothane induces liver disorder more often than enflurane. There are very few reports of fulminant hepatitis associated with isoflurane[32], a newly developed inhalation anesthetic that is considered to be less hepatotoxic than enflurane because both the metabolic rate and diminished rate of hepatic blood flow are lower[33–37].

For the past decade many anesthetists have used enflurane in place of halothane because they believed it less hepato-toxic without convincing studies. Our present study of PAMLD supports this tendency as reasonable.

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