Effects of repeat exposure to inhalation anesthetics on liver and renal function

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Abstract

Background: Cross hypersensitivity to inhalation anesthetics has not been studied. The aim of this study was to investigate it by comparing liver and renal function after repeated anesthesia with sevoflurane and isoflurane retrospectively.

Materials and Methods: The adult patients who received general anesthesia twice within the interval of 14 days to 1 year were retrospectively analyzed. Those who received sevoflurane anesthesia twice (SS group, 53 cases), isoflurane anesthesia twice (II group, 31 cases), sevoflurane followed by isoflurane anesthesia (SI group, 29 cases), isoflurane followed by sevoflurane anesthesia (IS group, 35 cases), and propofol–fentanyl anesthesia twice (PP group, 58 cases) were enrolled. Serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (Bil), gamma-glutamyl transpeptidase (γ-GTP), blood urea nitrogen (BUN), and creatinine (Cr) measured 1-3, 5-8, and 12-16 days after surgery were investigated.

Results: In the IS group, the number of the patients with abnormal values of ALT and γ-GTP 5–8 days after surgery were significantly smaller at second anesthesia compared to the first anesthesia. The number of the patients with abnormal values of AST, ALT, and γ-GTP were significantly larger in the II group than the SS and PP groups. The number of patients who had higher values in each parameter at second anesthesia compared to the first anesthesia was not different among the groups.

Conclusions: Sevoflurane and isoflurane might have no cross hypersensitivity. Both anesthetics might not have any additional risks to increase liver and renal damage by second anesthesia.

Key words: General anesthesia, isoflurane, kidney, liver, propofol, sevoflurane

Introduction

We had studied the effects of inhalation anesthetics on liver and renal function.[1,2] In these studies, isoflurane anesthesia increased the serum concentration of liver enzymes after surgery more than sevoflurane anesthesia. We had also shown that repeated sevoflurane or isoflurane anesthesia in 30-180 days had no risk for increasing liver and renal damage after the second anesthesia compared to the first one.[3]

Gunaratnam et al. reported a case of isoflurane hepatitis by cross hypersensitivity with halothane.[4] Ohmori et al.[5] reported a case who had significant increases of serum concentration of liver enzymes following sevoflurane anesthesia after isoflurane anesthesia. They suggested cross hypersensitivity to inhalation anesthetics by a drug-induced lymphocyte stimulating test. However, no studies have been performed to investigate cross hypersensitivity of sevoflurane and isoflurane. The present retrospective study was performed to investigate cross hypersensitivity by comparing liver and renal function after repeated anesthesia with sevoflurane and isoflurane in comparison with anesthesia with propofol.

Materials and Methods

After the review board approval, records of the adult (20-70 years) patients with ASA physical status I or II, who received general anesthesia twice within an interval of 14 days to 1 year in the periods between 1999 and 2007, were extracted. Patients who had a history of general anesthesia before these periods and alcohol, drug, or substance abuse, who had apparent liver or renal disease including viral hepatitis, or obesity (body mass index >30), and who received abdominal or thoracic (including cardiac) surgery were excluded. In addition, the patients who had episodes of critical hypotension (systolic blood pressure <60 mmHg
for more than 30 min) or hypoxia (oxygen saturation <80% for more than 30 min), and who had blood loss more than 2000 mL during surgery were also excluded. Those who received sevoflurane anesthesia twice (SS group), isoflurane anesthesia twice (II group), sevoflurane followed by isoflurane anesthesia (SI group), isoflurane followed by sevoflurane anesthesia (IS group), and propofol–fentanyl anesthesia twice (PP group) were enrolled in this study.

Serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (Bil), gamma-glutamyl transpeptidase (γ-GTP), blood urea nitrogen (BUN), and creatinine (Cr) measured 1-3, 5-8, and 12-16 days after surgery were analyzed. The number of the patients who had abnormally high values in these parameters was compared among the groups and between the first anesthesia and the second one.

All data are expressed as mean ± SD, number of the patients or median and range. The minimum alveolar concentration (MAC) hours were calculated from the end-tidal anesthetic concentration and the duration of exposure shown on the anesthesia record. Post hoc power analysis was performed for the c²-square test with effect size = 0.3 and α = 0.05 using G Power 3™ (University Mannheim, Germany). Statistical analysis was performed with analysis of variance (ANOVA) and repeated ANOVA followed by Bonferroni/Dunn test as a post hoc analysis for numerical data, and c²-square test for the number of the patients. A P value less than 0.05 was considered to be statistically significant.

**Results**

The power of this study was 0.934. There were some significant differences in duration of surgery and doses of anesthetics between the groups and between the first and second anesthesia [Table 1]. For induction of anesthesia, midazolam, thiopental, propofol, and/or fentanyl were used. As muscle relaxants, vecuronium and/or pancuronium was used. The doses of these agents had big variations and no significant differences among the groups (data not shown). Other demographic data were not different among the groups [Table 1].

**Table 1: Demographic data**

|                | SS          | II          | SI          | IS          | PP          |
|----------------|-------------|-------------|-------------|-------------|-------------|
| Age (years)    | 57±10       | 54±8        | 59±8        | 54±9        | 55±8        |
| Male/Female    | 33/20       | 15/16       | 20/9        | 18/17       | 25/33       |
| Body weight (kg)| 62±8       | 60±9        | 61±8        | 58±9        | 62±7        |
| Surgery, B/H/T/S|            |             |             |             |             |
| First          | 20/15/11/7  | 10/8/7/6    | 5/8/10/6    | 7/9/5/14    | 19/20/10/9  |
| Second         | 15/10/19/9  | 8/10/8/5    | 5/9/11/4    | 6/12/9/8    | 12/18/20/8  |
| Interval (days)| 76±67       | 91±84       | 90±86       | 80±90       | 77±75       |
| Duration of surgery (h) |          |             |             |             |             |
| First          | 332±86      | 324±96      | 318±110     | 312±129     | 325±141     |
| Second         | 222±61*     | 192±79*     | 188±67*     | 200±77*     | 185±71*     |
| Inhalation anaesthetic (MAC h) |          |             |             |             |             |
| First          | 4.3±0.86    | 3.8±0.91*   | 3.8±1.10*   | 3.9±1.10*   | NA          |
| Second         | 3.8±1.03*   | 3.2±1.26    | 2.8±0.98*,* | 3.4±1.27    | NA          |
| Total gas flow (L/m) |          |             |             |             |             |
| First          | 5 (3-6)     | 5 (3-6)     | 5 (3-6)     | 5 (3-6)     | 5 (3-6)     |
| Second         | 5 (3-6)     | 5 (3-6)     | 5 (3-6)     | 5 (3-6)     | 5 (3-6)     |
| \(O_2\) concentration (%) |          |             |             |             |             |
| First          | 41±7        | 41±8        | 40±7        | 40±6        | 38±6        |
| Second         | 41±7        | 38±7        | 42±6        | 42±7        | 41±7        |
| Propofol (mg)  |            |             |             |             |             |
| First          | 119±70*     | 122±75*     | 100±65*     | 99±77*      | 1658±484    |
| Second         | 104±71*     | 101±73*     | 102±73*     | 106±70*     | 1319±552*   |
| Fentanyl (µg)  |            |             |             |             |             |
| First          | 208±81*     | 173±48*     | 174±47*     | 157±56*     | 449±160     |
| Second         | 140±59*,*   | 102±52*,*   | 112±48*,*   | 120±57*,*   | 311±122*    |
| Blood transfusion (mL) |          |             |             |             |             |
| First          | 166±303     | 168±331     | 158±304     | 171±379     | 124±299     |
| Second         | 83±249      | 129±345     | 103±286     | 86±224      | 85±233      |

Mean±SD or number of the patients are shown. For total gas flow, median and range (in parenthesis) are shown. SS-first anesthesia, sevoflurane, second anesthesia, sevoflurane; II-first, isoflurane, second, isoflurane; SI-first, sevoflurane, second, isoflurane; IS-first, isoflurane, second, sevoflurane; PP-first, propofol-fentanyl, second, propofol-fentanyl, surgery, B=brain, H=head and neck=T , body surface=S, spine. *P<0.05 vs. 1st surgery; †P<0.05 vs. SS, †P<0.05 vs. PP
In the IS group, the number of the patients with abnormal values of ALT and γ-GTP 5-8 days after surgery were significantly smaller at second anesthesia compared to the first anesthesia [Table 2]. The number of the patients with abnormal values of AST, ALT, and γ-GTP were significantly larger in the II group than the SS and PP groups in both first and second anesthesia. The PP group had smaller number of the patients with abnormal values of AST and γ-GTP than the SS group. No clinical liver failure was recorded in the data analyzed. BUN showed abnormal values in a few patients, but clinically negligible. Cr was within the normal range in all patients. The number of the patients who showed higher values in the parameter at second anesthesia than at first anesthesia was not different among the groups [Table 3].

**Discussion**

This study showed that postoperative liver and renal damages did not increase by repeated anesthesia with either combination of sevoflurane and isoflurane as well as repeated propofol–fentanyl anesthesia in 14 days to 1 year. The number of the patients with abnormally high serum concentrations of liver enzymes was the largest in isoflurane in the anesthesia methods studied.

There are some limitations of this study. Being a retrospective study, we could not control perioperative managements such as antibiotics, fluid management, body temperature, respiration, etc., which might affect liver and renal functions. However, it is almost impossible to perform such a study prospectively because we cannot predict second anesthesia before the first one. In addition, we extracted all information from anesthesia and postoperative records, which might miss some information. We did not select the type of surgery because the patients received the same type of surgery twice were quite few. Therefore, there were some significant differences in duration of surgery and doses of anesthetics between the groups and between the first and second anesthesia. Duration of surgery and dose of anesthetics could have some effects on liver and renal functions. However, the type of surgery shown by the surgical site was not different among the groups, therefore, the groups were comparable regarding type of surgery. We excluded abdominal and thoracic surgery, which are considered to have a great effect on liver and renal functions. Surgical procedures might not have a great effect on liver and renal functions. Total fresh gas flow between 3 and 6 L/min was used in this study. Therefore, the results might be different from using lower total fresh gas flow, which is increasingly used recently.

We extracted records of repeated anesthesia from 14 days to 1 year because peak increases in serum concentration of liver enzymes was the largest in isoflurane in the anesthesia methods studied.

### Table 2: Liver and renal function test

|            | SS (n=53) | II (n=31) | SI (n=29) | IS (n=35) | PP (n=58) |
|------------|-----------|-----------|-----------|-----------|-----------|
| ALT first  |           |           |           |           |           |
| 1          | 1         | 2         | 1         | 2         | 1         |
| 2          | 0         | 0         | 0         | 0         | 0         |
| 3          | 0         | 0         | 0         | 0         | 0         |
| ALT second |           |           |           |           |           |
| 1          | 2         | 1         | 1         | 2         | 3         |
| 2          | 1         | 2         | 2         | 0         | 1         |
| 3          | 0         | 0         | 0         | 0         | 0         |
| AST first  |           |           |           |           |           |
| 1          | 2         | 1         | 1         | 2         | 1         |
| 2          | 0         | 0         | 0         | 0         | 0         |
| 3          | 0         | 0         | 0         | 0         | 0         |
| AST second |           |           |           |           |           |
| 1          | 2         | 1         | 1         | 2         | 3         |
| 2          | 1         | 2         | 2         | 0         | 1         |
| 3          | 0         | 0         | 0         | 0         | 0         |
| BUN first  |           |           |           |           |           |
| 1          | 1         | 1         | 1         | 1         | 1         |
| 2          | 0         | 0         | 0         | 0         | 0         |
| 3          | 0         | 0         | 0         | 0         | 0         |
| BUN second |           |           |           |           |           |
| 1          | 1         | 1         | 1         | 1         | 1         |
| 2          | 0         | 0         | 0         | 0         | 0         |
| 3          | 0         | 0         | 0         | 0         | 0         |
| Cr first   |           |           |           |           |           |
| 1          | 0         | 0         | 0         | 0         | 0         |
| 2          | 0         | 0         | 0         | 0         | 0         |
| 3          | 0         | 0         | 0         | 0         | 0         |
| Cr second  |           |           |           |           |           |
| 1          | 0         | 0         | 0         | 0         | 0         |
| 2          | 0         | 0         | 0         | 0         | 0         |
| 3          | 0         | 0         | 0         | 0         | 0         |

The numbers of the patients with the value over the normal range are shown. In the parentheses, the numbers of the patients with the value over two times of the normal range are shown. 1, 1-3 days; 2, 5-8 days; 3, 12-16 days. SS, first anesthesia, sevoflurane, second anesthesia, sevoflurane; II, first, isoflurane, second, isoflurane; SI, first, sevoflurane, second, isoflurane; IS, first, isoflurane, second, sevoflurane; PP, first, propofol–fentanyl, second, propofol–fentanyl, AST=aspartate aminotransferase, ALT=alanine aminotransferase, Bil=total bilirubin, γ-GTP=glutamyl transpeptidase, BUN=blood urea nitrogen, Cr=creatinine, M=male, F=female, *P<0.05 vs. first surgery, †P<0.05 vs. SS, ‡P<0.05 vs. PI, §P<0.05 vs. II, **P<0.05 vs. SI.
enzymes were observed within 14 days postoperatively in our previous studies,[1,2,3,6] and it is well known that the risk of halothane hepatitis increased by repeated anesthesia in 1 year.

For renal function, only serum concentrations of BUN and Cr were investigated in this study because this is a retrospective study and we did not measure other renal parameters routinely. Many studies investigated urinary enzymes as a sensitive marker of renal tubular damage. In our previous studies, transient increases in urine protein and glucose,[3] serum and urine β₂-microglobulin, and urine N-acetyl-β-d-glucosaminidase[6] were observed after sevoflurane or isoflurane anesthesia, while no clinical renal damage was observed. Higuchi et al.[7] reported that these sensitive markers might not be adequate, while BUN and Cr had already been confirmed of their role to indicate renal function. Therefore, BUN and Cr were enough to investigate renal function clinically.

Our previous studies[2,3] showed that isoflurane anesthesia induces a greater increase in serum concentrations of liver enzymes compared to sevoflurane anesthesia. These are consistent with the current results. Several reasons of liver damage by isoflurane anesthesia have been proposed. Liver blood flow might not attribute to the difference in liver damage between sevoflurane and isoflurane anesthesia, because both anesthetics have the same impact in liver blood flow.[8,9] Laizzo et al.[10] suggested that isoflurane modifies G-protein of α₁-receptor of the cell membrane, which induces calcium release from endoplasmic reticulum into cytosol. The accumulation of calcium induces liver damage. A metabolite of isoflurane, trifluoro acetic acid (TFA) combines with intracellular protein and may induce immune reaction to produce liver damage like halothane.[11] Many factors such as antibiotics, other drugs, or fluid infusion administered postoperatively might have some effects on liver function. It was difficult to analyze completely all these factors in the record, but no remarkable differences in these factors seemed to be observed among the groups.

TFA might induce hypersensitivity to increase liver enzymes after second exposure to isoflurane.[12] Sevoflurane is metabolized to hexafluorosopropanol, inorganic fluoride, and formaldehyde. As the drug, apparently, sevoflurane does not seem to form TFA, it is usually not considered to induce immune-mediated liver injury as previously observed with other inhalation anesthetics.[13] However, cross hypersensitivity between isoflurane and sevoflurane cannot be excluded.[5] It is reported that a second exposure to halothane or enflurane induces more liver damage than the first one.[14] Zizek et al. reported subacute liver failure after repeated sevoflurane anesthesia.[15] Repeated sevoflurane anesthesia did not change metabolism of sevoflurane and induced no renal damage, while two of eight patients had increased concentration of liver enzymes after anesthesia, especially after second time in one case in the study by Takenami et al.[16] In 27 cases of 80 repeated sevoflurane anesthesia, 11 liver damage and 5 renal damage were suspected, but all were transient and were not clinically significant.[17] In monkeys, multiple administration of sevoflurane increased serum concentration of liver enzymes at 1 week and it returned to the baseline at 2 weeks without any pathological liver damages.[18] Moreover, repeated low flow sevoflurane anesthesia with the interval of 7 days in beagles did not affect liver and renal function.[19] In the prospective human study of repeated sevoflurane anesthesia, the multiple administration of sevoflurane anesthesia was not related to adverse effects of liver and renal damage.[17] Repeated isoflurane anesthesia did not produce liver and renal damage in an animal study,[20] while Brunt et al. reported a case with liver damage by repeated isoflurane anesthesia.[21] Our previous studies[3,6] and present results showed that repeated sevoflurane or isoflurane anesthesia did not increase liver or renal damage. Therefore, it might be only a rare occasion to

### Table 3: Comparison between the first and second anesthesia

|          | SS (n=53) | II (n=31) | SI (n=29) | IS (n=35) | PP (n=58) |
|----------|-----------|-----------|-----------|-----------|-----------|
| AST      | 1         | 0         | 1         | 0         | 0         |
|          | 2         | 2         | 2         | 2         | 1         |
|          | 3         | 1         | 1         | 0         | 0         |
| ALT      | 1         | 0         | 1         | 0         | 0         |
|          | 2         | 2         | 2         | 2         | 1         |
|          | 3         | 0         | 1         | 1         | 0         |
| Bil      | 1         | 0         | 0         | 0         | 0         |
|          | 2         | 0         | 0         | 0         | 0         |
|          | 3         | 0         | 0         | 0         | 0         |
| γ-GTP    | 1         | 1         | 1         | 0         | 0         |
|          | 2         | 1         | 2         | 1         | 2         |
|          | 3         | 0         | 1         | 0         | 0         |
| BUN      | 1         | 0         | 0         | 0         | 0         |
|          | 2         | 0         | 0         | 0         | 0         |
|          | 3         | 0         | 0         | 0         | 0         |
| Cr       | 1         | 0         | 0         | 0         | 0         |
|          | 2         | 0         | 0         | 0         | 0         |
|          | 3         | 0         | 0         | 0         | 0         |

The number of the patients with the higher value after second anesthesia compared to that after first anesthesia are shown. 1, 1-3 days; 2, 5-8 days; 3, 12-16 days. SS, first anesthesia, sevoflurane, second anesthesia, sevoflurane; II, first, isoflurane, second, isoflurane; SI, first, sevoflurane, second, isoflurane; IS, first, isoflurane, second, sevoflurane; PP, first, propofol-fentanyl, second, propofol-fentanyl. AST=aspartate aminotransferase, ALT=alanine aminotransferase, Bil=total bilirubin, γ-GTP=γ-glutamyl transpeptidase, BUN=blood urea nitrogen, Cr=creatinine, no significant differences were observed among the groups.
have liver damage after repeated sevoflurane or isoflurane anesthesia.

To the best of our knowledge, no studies have been performed on cross hypersensitivity between sevoflurane and isoflurane anesthesia except for a case report by Ohmori et al. The drug-induced lymphocyte stimulating test in their case showed positive results for halothane, sevoflurane, and isoflurane, and pseudo-positive for enflurane, which suggested cross hypersensitivity in inhalation anesthetics. However, the present results did not show any increase in liver damage after second anesthesia in IS and SI groups.

In conclusion, sevoflurane and isoflurane might have no cross hypersensitivity to induce liver damage. Both anesthetics might not have any additional risks to increase liver and renal damage after second anesthesia.

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