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Correlation between renal function and pharmacokinetic parameters of inorganic fluoride following sevoflurane anesthesia

TOMOKI NISHIYAMA[1] and NARUSHI TODA[2]

[1] Department of Anesthesiology, JR Tokyo General Hospital, 2-1-3 Yoyogi, Shibuya-ku, Tokyo, 151 Japan
[2] Department of Anesthesiology, Kagawa Rosai Hospital, 3-3-1 Jyouto-cho, Marugame, Kagawa, 763 Japan

Abstract: We studied the correlation between renal function and pharmacokinetic parameters of inorganic fluoride following sevoflurane anesthesia. In 30 neurosurgical patients aged 40–70 years, anesthesia was induced with midazolam and sevoflurane and maintained with sevoflurane and nitrous oxide in oxygen. Serum and urine inorganic fluoride (F^-) levels and β_2-microglobulin (BMG), blood urea nitrogen (BUN), and serum creatinine (Cr) were measured during and after anesthesia. The decrease rate of serum F^- level and the area under the curve (AUC) of serum F^- were calculated. Correlations among sevoflurane dosage, duration of administration, peak serum F^- level, AUC, the decrease rate of serum F^- level, and the maximum values in BUN, Cr, and urine BMG during the study were investigated. Urine BMG increased significantly after surgery but returned to the preoperative level in a week. BUN, Cr, and serum BMG remained within normal ranges during the study. Sevoflurane dosage and duration of administration were significantly correlated with AUC and the maximum value of urine BMG, but not with the peak serum F^- level or the decrease rate of serum F^-. AUC was significantly correlated with the maximum value of urine BMG. In sevoflurane anesthesia, sevoflurane dosage, duration of administration, and AUC affected urine BMG level, but not peak serum F^-.

Key words: Sevoflurane, Renal function, β_2-Microglobulin, Inorganic fluoride

Introduction

Sevoflurane contains seven fluorine atoms [1]. One of them is released when sevoflurane is metabolized and it may cause renal damage [2]. There are many reports on serum inorganic fluoride (F^-) and renal function in sevoflurane anesthesia [2–4]. However, few studies have evaluated the influence of F^- on renal function. In this study, we investigated the relationships between renal function and the duration of sevoflurane administration, serum F^- levels, the decrease rate of serum F^- levels, and the area under the curve (AUC) of serum F^- levels.

Address correspondence to: T. Nishiyama
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Materials and methods

Thirty patients (18 men and 12 women) without a history of renal or hepatic disease were investigated. The study protocol was approved by the ethics committee of our hospital, and informed consent was obtained from each patient. The average age of the patients was 60 ± 11 [mean ± standard deviation (SD)] years (range: 40–70 years), and the average body weight was 60.9 ± 9.5 kg (range: 44–80 kg). Eight patients underwent cerebrovascular surgery and 22 underwent tumor resection. None of the patients had received drugs associated with hepatocellular enzyme induction, corticosteroids, or diuretics before surgery.

Atropine 5 $\mu g \cdot kg^{-1}$ and midazolam 0.05 $mg \cdot kg^{-1}$ were administered intramuscularly 15 min before entering the operating room. Anesthesia was induced with midazolam 0.1 $mg \cdot kg^{-1}$ and sevoflurane 2%. Endotracheal intubation was facilitated with vecuronium 0.15 $mg \cdot kg^{-1}$. Anesthesia was maintained with sevoflurane 1% to 2% and 3 $l \cdot min^{-1}$ of nitrous oxide in 2 $l \cdot min^{-1}$ of oxygen. Each patient was initially ventilated at 10 $ml \cdot kg^{-1}$, 10 $breaths \cdot min^{-1}$, after which ventilation rates were adjusted to maintain $Paco_2$ within the range 30–35 mmHg. In all patients, 300 ml of 20% mannitol was infused at the beginning of craniotomy.

Sevoflurane dosage was expressed as minimum alveolar concentration (MAC)-hours. End-tidal concentration of 2.05% was evaluated as 1 MAC. Serum and urine F^- levels were measured using a Microprocessor Ionalyser (Orion Research, Boston, MA, USA, detec-

tion limit >1.0 X 10^{-3} μmol·l^{-1}) immediately after the start of anesthesia, at 3 and 6 h of anesthesia, immediately after cessation of sevoflurane inhalation, and at 1, 3, 5, 12, and 20 h after anesthesia. Serum and urine β_2-microglobulin (BMG) levels were measured by immunoturbidometry (LPIA-100, Diatron, Tokyo, Japan, detection limit >0.4 mg·l^{-1}).

Serum and urine BMG levels, blood urea nitrogen (BUN), and serum creatinine (Cr) were measured before and 1, 3, and 7 days after anesthesia. Urine collected during a 1-h period in each measurement point was used for urine analysis. On the 1st, 3rd, and 7th postoperative day (POD), blood and urine were collected at 8:00 a.m. The rate of decrease of serum F^- levels was calculated using the values obtained at six measurement points from the end of sevoflurane inhalation to 20 h after the end of inhalation by the least-squares method. AUC was also calculated from the start of anesthesia.

Sevoflurane dosage, duration of administration, peak serum F^- level, AUC, and the decrease rate of serum F^- level were compared against the maximum BUN, Cr, and urine BMG values during the study using Spearman's rank-correlated index. The correlation between sevoflurane dosage or duration of administration and peak serum F^- level was also calculated using the same analysis.

Statistical analysis was performed with analysis of variance (ANOVA) with repeated measures for the variation in the groups. $P < 0.05$ was considered statistically significant. All values are expressed as mean ± SD.

Results

The duration of anesthesia was 518 ± 197 min (range: 240–1010 min), the duration of surgery was 412 ± 195 min (range: 125–905 min), and the duration of sevoflurane administration was 472 ± 198 min (range: 150–960 min). The sevoflurane dosage was 4.9 ± 1.8 MAC·h (range: 1.6–11.9 MAC·h). The crystalloid infusion volume was 2349 ± 855 ml, urine output was 1087 ± 668 ml, and mean surgical blood loss was 500 ± 467 ml. No blood transfusions were performed.

The peak serum F^- levels were 22.6–64.2 μmol l^{-1}, and 13 patients had peak serum F^- levels exceeding 50 μmol·l^{-1} (Fig. 1). The decrease rate of serum F^- levels was 1.81 ± 0.7 μmol·l^{-1}·h^{-1}, and AUC was 958 ± 416 μmol·l^{-1}·h^{-1}. Urine F^- levels fluctuated widely in individual patients and over time (Fig. 1).

Renal function tests are shown in Fig. 2. Urine BMG levels increased significantly compared with preanesthetic values on the 1st and 3rd PODs. BUN, Cr, and serum BMG were within the normal ranges during the study. No clinically significant renal dysfunction was seen in any of the patients.

The correlations in each parameter are shown in Tables 1 and 2. The sevoflurane dosage and duration of administration were significantly correlated with AUC and the maximum value of urine BMG, but not with the peak serum F^- level, the rate of decrease of serum F^-, or the maximum values of BUN or Cr. AUC was significantly correlated with the maximum value of urine BMG, but not with the maximum values of BUN or Cr.

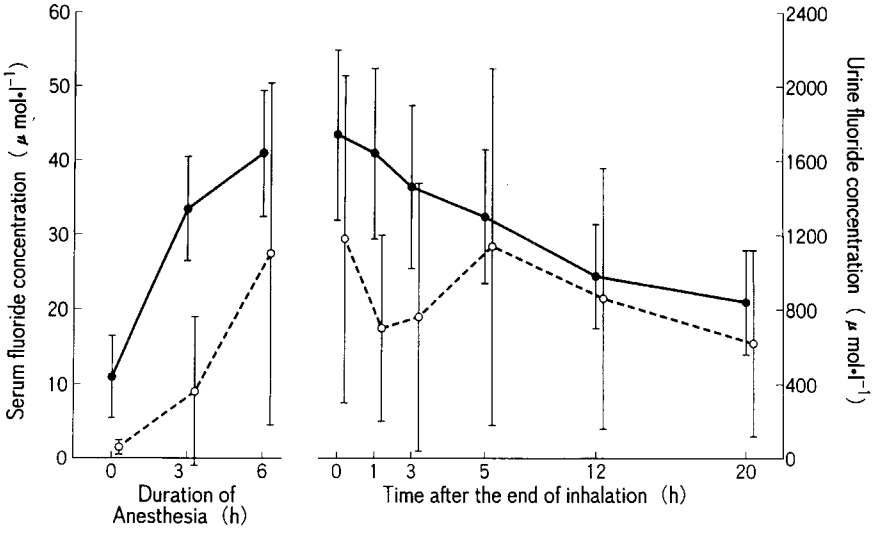

Fig. 1. Serum and urine inorganic fluoride concentrations. Serum concentrations are shown in *closed circles*, and urine concentrations are shown in *open circles*. *Bars* indicate SD

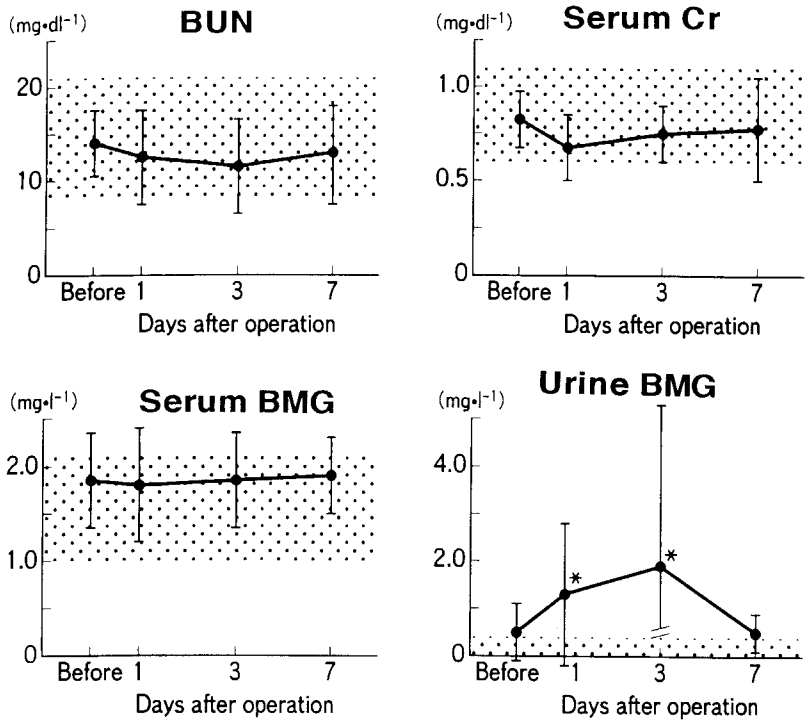

Fig. 2. Indices in renal function *Bars* indicate SD. The *shaded area* shows the normal range. * $P < 0.05$ vs. before surgery. BUN, blood urea nitrogen; Cr, creatinine; BMG, β_2-microglobulin

Table 1. Correlations between indexes of renal function and sevoflurane dosage, duration of administration and serum inorganic fluoride

	BUN[a]	Cr[a]	Urine BMG[a]
Sevoflurane dosage (MAC·h)	−0.0078	0.1074	0.5832**
Duration of sevoflurane administration (h)	−0.0849	−0.0326	0.3830*
Peak serum F^- level ($\mu mol \cdot l^{-1}$)	−0.1167	0.1622	0.2853
AUC	0.0468	0.3126	0.5783**
Decrease rate of serum F^- level ($\mu mol \cdot l^{-1} \cdot h^{-1}$)	−0.3008	0.0619	0.1368

BUN, blood urea nitrogen; Cr, creatinine; BMG β_2-microglobulin, AUC, Area under the curve; MAC, minimum alveolar concentration.
* $P < 0.05$, ** $P < 0.01$ by Spearman's rank-correlated index.
[a] Maximum values.

Table 2. Correlations between parameters in serum inorganic fluoride and sevoflurane dosage and duration of administration

	Peak serum F^- level	AUC	Decrease rate of serum F^- level
Sevoflurane dosage	0.3635*	0.6648*	−0.1546
Duration of sevoflurane administration	0.2580	0.5365**	−0.0048

AUC, Area under the curve.
* $P < 0.05$, ** $P < 0.01$ by Spearman's rank-correlated index.

Discussion

It has been reported that elevated serum F^- levels might cause polyuric renal insufficiency after methoxyflurane anesthesia [5], and renal insufficiency might result when serum F^- levels exceed 50 $\mu mol\ l^{-1}$ [6]. Sevoflurane produces F^- as a metabolite [7] as with methoxyflurane. However, nephrotoxicity has not been demonstrated following sevoflurane anesthesia when serum F^- levels exceeded 50 $\mu mol \cdot l^{-1}$ [3]. In this study, no renal damage occurred clinically in patients whose peak serum F^- levels exceeded 50 $\mu mol \cdot l^{-1}$. With methoxyflurane anesthesia, the half-life of serum F^- is about 48 h [8], so serum F^- levels over 50 $\mu mol \cdot l^{-1}$ are maintained for a considerable duration. On the other hand, the serum elimination half-life of serum F^- following sevoflurane anesthesia is reported to be 34 h [9], and in the present study it was calculated to be 15.4 h based on the decrease rate of serum F^- levels. The shorter half-life of serum F^- after sevoflurane anesthesia compared to that with methoxyflurane anesthesia reduces exposure of the kidney to F^-. This may be why renal damage does not occur with sevoflurane anesthesia even when peak serum F^- levels exceed 50 $\mu mol \cdot l^{-1}$. In this study, we measured the decrease rate of serum F^- levels and AUC as indicators of renal exposure to F^-.

Kobayashi et al. [3] and Frink et al. [4] reported that the sevoflurane dosage was significantly correlated with peak serum F^- levels. In their studies, no renal dysfunction occurred even if serum F^- levels exceeded 50 $\mu mol \cdot l^{-1}$ [3], but they examined only BUN, Cr, serum

electrolytes, and urine volume or urine specific gravity. In our investigation, we examined BMG as an indicator of renal tubular function. We found that the peak serum F^- level was correlated only with the sevoflurane dosage; however, AUC correlated well with sevoflurane dosage, duration of sevoflurane administration, and the maximum value of urine BMG. This indicates that AUC is a better indicator of renal exposure to F^- than the peak serum F^- level.

Kumano et al. [10] reported that no renal damage occurred following sevoflurane anesthesia for about 2 h. However, in their report, urine BMG and N-acetyl-β-D-glucosaminidase on the 1st POD increased over the normal range, which suggested renal tubular damage. In the present study, urine BMG increased beyond the normal range on the 1st and 3rd PODs and returned to the preoperative level on the 7th POD. It was suggested that renal tubular damage occurred transiently but recovered in a week. This was supported by the study performed by Kanematsu [11]. He reported that sevoflurane anesthesia in rats produced disarrangement of the brush border, enlargement of the mitochondria, and disturbance of the basement membranous villi on electron microscopy. However, these changes were reversible in a week, and no remarkable changes were seen on light microscopy. As in the present study, BUN and Cr did not increase in his study. Therefore, transient renal tubular injury is not always followed by renal damage.

In conclusion, we found that sevoflurane dosage, duration of administration and AUC but not the peak serum F^- level correlated with the maximun urine BMG level. Elevated urine BMG levels, which suggest renal tubular injury, normalized within 7 days. There was no clinical evidence of renal damage.

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