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Transient renal tubular dysfunction in a patient with severe asthmatic attack treated with sevoflurane

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Introduction

Inhalational anesthetics are effective in treating severe asthmatic attacks resistant to ordinary medical therapies. Since sevoflurane exerts a strong bronchodilating effect and is less irritating to the airway [1], the drug is effective in treating asthmatic attacks [2]. However, the possibility of renal impairment due to long-term sevoflurane administration remains controversial [3]. We report a patient who had a severe asthmatic attack, was treated by inhalation of sevoflurane for 9 days in our intensive care unit (ICU) and developed transient renal tubular dysfunction.

Case report

A 62-year-old man with a 10-year history of asthma had a severe asthmatic attack. The study was approved by the ethical committee of the hospital and informed consent was obtained from the patient and his family on a collection of blood and urine. He resisted ordinary medical treatments and gradually lost consciousness. Oxygen 5 l·min^{-1} was administered with an oxygen mask to the patient, and arterial blood gas analysis showed the pH, PaO_2, $PaCO_2$, HCO_3^-, and Base Excess (BE) to be 7.256, 40.9 mmHg, 64.2 mmHg, 28.5 mmol·l^{-1}, and -0.3 mEq·l^{-1}, respectively, at the time of admission to the ICU. He was intubated and mechanically ventilated. Isoflurane was used for a total of 9 h on the first and second hospital days. However, because isoflurane could not reduce the irritability of his airway, the control of ventilation was difficult with isoflurane. We therefore replaced the drug with sevoflurane. Inhalation anesthetics were passed from a vaporizer and added to a humidifier system attached to a ventilator (Puritan-Bennett 7200ae). Soda lime was not used. Inhaled isoflurane and sevoflurane concentration varied between 0.25% and 6.0% to provide bronchodilation. The end-tidal concentrations of the inhalation anesthetics were continuously measured with an anesthetic analyzer (Capnomac, DATEX, Helsinki). The minimum alveolar concentration (MAC) hours of administered sevoflurane was 298 MAC hours. The age-corrected MAC of sevoflurane in this case was 1.3%. Figure 1 shows the serum and urinary inorganic fluoride concentrations during and after the administration of sevoflurane. The serum inorganic fluoride concentration increased to over 50 μmol·l^{-1}, and its maximum level was 70.5 μmol·l^{-1}. The maximum urinary inorganic fluoride concentration was 2047 μmol·l^{-1}. During sevoflurane administration, the urinary inorganic fluoride concentration did not decrease. Figure 2 plots the urinary concentrations of *N*-acetyl-β-D-glucosaminidase (NAG) and β-2-microglobulin (BMG). The urinary NAG and BMG concentrations were abnormally elevated, and their maximum levels were 52.3 U·l^{-1} and 86 000 μg·l^{-1}. These concentrations decreased gradually from the 15th day. The serum BMG concentration was in the normal range (data not shown). Figure 3 shows the data on the urinary volume and daily urinary excretion of NAG and BMG. The daily excretion of NAG and BMG was abnormally elevated, reaching a maximum of 137.5 U·day^{-1} and 238.7 mg·day^{-1}, respectively. The volume of urine was large (2–61 daily), but its specific gravity was in the normal range. The values of blood urea netroge (BUN), serum creatinine, and creatinine clearance were normal. In the phenolsulfonphthalein (PSP) excretion test, the value at 15 min

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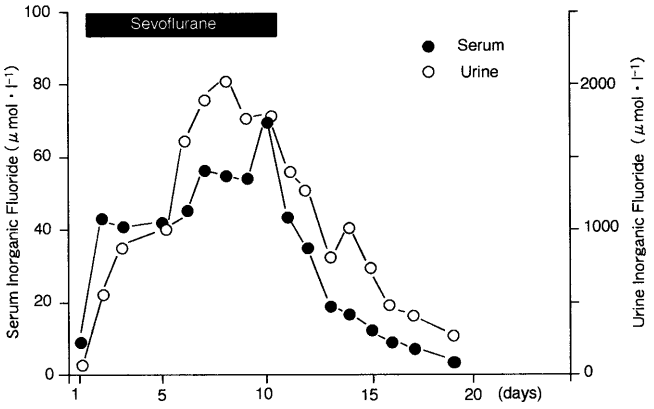

Fig. 1. Concentrations of serum and urinary inorganic fluoride. *Closed circles* and *open circles* indicate the serum and urinary inorganic fluoride concentrations, respectively. The serum inorganic fluoride concentration increased to over 50 μmol·l^{-1}, and its maximum level was 70.5 μmol·l^{-1}. The maximum urinary inorganic fluoride concentration was 2047 μmol·l^{-1}

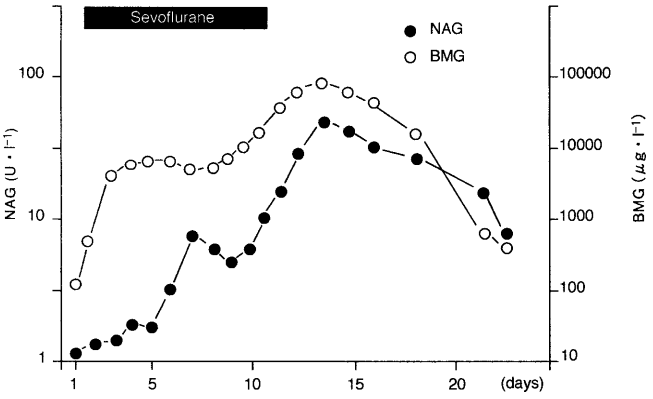

Fig. 2. Concentrations of urinary *N*-acetyl-β-D-glucosaminidase (NAG) and β-2-microglobulin (BMG). The abscissae are logarithmic scales. *Closed circles* and *open circles* indicate urinary NAG and BMG concentrations, respectively. Urinary NAG concentration increased after the 7th day, and its maximum level was 52.3 U·l^{-1} on the 14th day. Urinary BMG concentration increased after the 2nd day, reaching a maximum of 86000 μg·l^{-1} on the 14th day

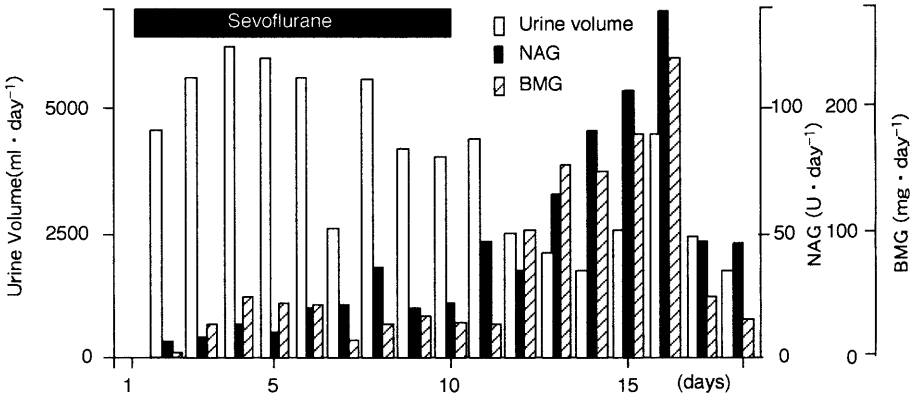

Fig. 3. Urine volume and daily excretion of urinary NAG and BMG. The urine volume was 2–61 daily. The daily urinary excretion of NAG increased after the 6th day, peaking at 137.5 U·day^{-1} on the 16th day. The daily urinary excretion of BMG increased after the 2nd day, peaking at 238.7 mg·day^{-1} on the 16th day

dropped to 17.4% on the 19th hospital day after admission but returned to the normal level on the 23rd hospital day. We administered cefazolin (CEZ), piperacillin (PIPC), fosfomycin (FOM), and gentamicin (GM) to prevent pneumonia in the ICU. The patient was weaned from the ventilator on the 16th hospital day and left the ICU on the 19th hospital day.

Discussion

Renal tubular dysfunction is observed when the serum inorganic fluoride concentration exceeds 50 μmol·l^{-1} during methoxyflurane anesthesia [4]. Methoxyflurane is mainly metabolized to inorganic fluoride by cytochrome P450 2E1 in the liver and kidney. Sevoflurane is similarly metabolized to inorganic fluoride by the same enzyme in the liver [5,6]. However, even when the serum inorganic fluoride concentration exceeds 50 μmol·l^{-1} in prolonged sevoflurane anesthesia, no clear renal dysfunction is observed [7,8]. The reason that there is no apparent toxicity in sevoflurane anesthesia irrespective of the compatible peak serum concentration might be the different site of metabolism and the shorter exposure time to an inorganic fluoride level over 50 μmol·l^{-1} compared with methoxyflurane anesthesia. No nephrotoxicity was observed in a patient who was treated with 104 h of inhalation of sevoflurane for an asthmatic attack [2]. However, in that report, the renal function was evaluated by the BUN and serum creatinine values, which mainly indicate renal glomerular function. We evaluated the renal glomerular function using the urine volume and the BUN, serum creatinine, and urinary fluoride concentrations as markers. We assessed renal tubular function on the basis of the urinary concentrations, daily excretion of

NAG and BMG, and the PSP excretion test. We administered sevoflurane to the patient for 9 days. Accordingly, sevoflurane was administered for 298 MAC hours, and the serum inorganic fluoride level exceeded 50 μmol·l^{-1} for more than 72 h. In this case, the longer exposure time to a high inorganic fluoride level may have caused the renal tubular dysfunction observed.

No decrease in the urine volume and no elevation of the BUN and serum creatinine values were observed. The creatinine clearance was also normal. The concentration of urinary inorganic fluoride did not decrease during administration of sevoflurane. Therefore, it is considered that renal glomerular function was probably not impaired in the case. The urine volume was 2–6 l·day^{-1}. Because we administered dopamine, polyuria was probably not caused by the renal tubular dysfunction. BMG is a serum protein of 11 800 molecular weight, and it can easily pass outside the renal glomeruli. However, since BMG is almost completely reabsorbed in the proximal tubular segments, its urinary excretion is very small in the normal kidney. When the serum BMG concentration increases or the renal tubules become injured, the urinary BMG excretion will increase. NAG is a glucoproteinase contained in renal tubular cells and is released in the urine at the time of renal tubular injury. Transient elevation of the urinary NAG and BMG levels after sevoflurane anesthesia has been reported [9–11]. In our patient, the urinary BMG concentration and excretion increased immediately after sevoflurane inhalation. When the serum inorganic fluoride concentration exceeded 50 μmol·l^{-1}, the urinary NAG concentration and excretion increased rapidly. The rises in these concentrations persisted for several days after the discontinuation of sevoflurane and after the serum inorganic fluoride concentration had decreased. The PSP excretion test reflects the renal blood flow or proximal tubular function. PSP excretion was decreased on the 19th hospital day. Since the urinary BMG and NAG excretions increased and the PSP excretion test showed a low value, it is considered that transient renal tubular dysfunction occurred in this patient.

While the patient was in the ICU, he received various medications. The antibiotics used were CEZ, PIPC, FOM, and GM. Other drugs that might influence the renal function were aminophylline, furosemide, dopamine, epinephrine, and isoflurane. GM was administered for 4 days from the 13th hospital day. Isoflurane was used for a total of 9 h on the first and second hospital days but was not used thereafter. The metabolism rate of isoflurane is low, and the volume of inorganic fluoride produced is small. Thus, it is considered that isoflurane had little influence on the renal tubular dysfunction in the case. Compound A has been indicated as the cause of nephrotoxicity in sevoflurane anesthesia. Because we did not use soda lime in this patient, compound A was not produced. However, since sevoflurane originally contains a very small quantity of compound A, we have to consider its effects. Hypoxemia might contribute to the elevation of the urinary BMG concentration in the early period. We think that inorganic fluoride as a metabolite of sevoflurane, hypoxemia, GM, and compound A as a combination might have been a cause of the transient renal tubular dysfunction.

Halothane, sevoflurane, and isoflurane can reduce airway resistance equally. It is reported that isoflurane is the best anesthetic for use in asthmatics because of its low metabolism [12]. Therefore, we choose isoflurane at first, but isoflurane exerts an irritating effect on the airway, and it was very difficult to use in our patient as well. Sevoflurane has a higher rate of metabolism than isoflurane [13], but it is less irritating to the airway. Therefore, we usually choose sevoflurane in a case of severe asthmatic attack at first.

In summary, we reported a patient who had a severe asthmatic attack and was treated by inhalation of 298 MAC hours sevoflurane for 9 days. However, only transient renal tubular dysfunction was observed. We think sevoflurane is a very useful and safe inhalation anesthetic for treating severe asthmatic attacks, but we must pay attention to its potential toxic effect on renal tubular function.

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