J Anesth (2002) 16:17–22

Journal of
Anesthesia

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Renal function in surgical patients after administration of low-flow sevoflurane and amikacin

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Abstract

Purpose. Compound A, a degradation product of sevoflurane, is nephrotoxic in rats, while aminoglycosides induce nephrotoxic injury in humans. Combining an aminoglycoside with a known nephrotoxin can enhance nephrotoxicity. We investigated the effects of aminoglycosides on renal function in surgical patients anesthetized with low-flow sevoflurane.

Methods. We compared the urinary excretion of several biochemical markers (such as total protein, albumin, β_2-microglobulin, glucose, and *N*-acetyl-β-glucosaminidase [NAG]) in an amikacin group ($n = 18$) and a control group ($n = 19$) of surgical patients anesthetized with low-flow anesthesia ($1 l \cdot min^{-1}$) with sevoflurane. All patients received cefotiam as an antibiotic perioperatively. In addition, the amikacin group received amikacin, an aminoglycoside, given intravenously twice a day (400 mg per day) from immediately after the induction of anesthesia to day 2 after anesthesia.

Results. Duration of anesthesia and mean compound A concentration were 5.2 ± 1.4 h and 27.2 ± 8.7 ppm (mean ± SD) in the amikacin group, and 5.1 ± 1.7 h and 27.1 ± 7.8 ppm in the control group respectively ($P > 0.05$). The two groups did not differ in clinical laboratory baseline values (blood urea nitrogen and serum creatinine concentration). There were no significant differences between the groups in either the maximum or the average values for the urinary excretion of biochemical markers after anesthesia.

Conclusion. Our study demonstrates that there is no synergic effect of compound A and amikacin on nephrotoxicity in humans.

Key words Anesthetics · Volatile sevoflurane · Degradation product: compound A · Toxicity: renal · Antibiotics: amikacin

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Received: February 14, 2001 / Accepted: August 10, 2001

Introduction

Compound A is a degradation product of sevoflurane, produced by the action of carbon dioxide absorbents on sevoflurane [1]. Compound A is nephrotoxic in rats, producing transient swelling and/or necrosis and associated renal tubular epithelial hyperplasia in the corticomedullary junction [2–4]. Whether compound A is toxic in humans is still unclear [3–10]. Some studies have recently reported, however, that increased urinary excretion of protein and glucose, indicative of nephrotoxicity, was present in volunteers and surgical patients after prolonged low-flow sevoflurane anesthesia [7,9,10].

Aminoglycosides remain widely used for the treatment of gram-negative bacillary infections [11]. They also damage the proximal renal tubule in humans [11]. The combined nephrotoxicity of antibiotics and volatile anesthetics in humans has been reported [12–14]. The present study investigated the effects of aminoglycosides on renal function in surgical patients anesthetized with low-flow sevoflurane.

Methods

The study was conducted at the Self Defense Force Central Hospital (SDFCH) in Tokyo, Japan, and was approved by the hospital Ethics Committee. An informed consent form was signed by each patient prior to participation in the study. The patients were 37 men undergoing anesthesia for orthopedic surgery. Patients whose medical history, physical examination, or laboratory tests showed evidence of abnormal hepatic or renal function were excluded from the study. The sample size of the current study was determined by power analysis ($\alpha = 0.05$; $\beta = 0.20$) to reveal a significant difference in the excretion of protein. Power analysis indicated that 18 patients per group were required to obtain a

significant difference, assuming that the standard deviations were 160 and the difference between the groups was 150 mg/day.

Patients were randomly assigned to one of two groups: the amikacin group ($n = 18$) and the control group ($n = 19$). All patients received cefotiam as an antibiotic twice a day (2.0 g per day i.v.) from immediately after the induction of anesthesia to day 2 after anesthesia. Subsequently, 600 mg of cefotiam was given orally for 5 days. In addition, the amikacin group received amikacin, an aminoglycoside, twice a day (400 mg per day i.v.) from immediately after the induction of anesthesia to day 2 after anesthesia.

Thirty minutes after receiving an intramuscular injection of atropine (0.5 mg) and midazolam ($0.08\,mg{\cdot}kg^{-1}$), each patient received an intravenous injection of thiopental ($3–5\,mg{\cdot}kg^{-1}$) and succinylcholine ($1\,mg{\cdot}kg^{-1}$) or vecuronium bromide ($0.1\,mg{\cdot}kg^{-1}$) to facilitate tracheal intubation. After tracheal intubation, anesthesia was maintained with sevoflurane, air, and oxygen (FiO_2, 0.4) at a total flow of $6\,l{\cdot}min^{-1}$. After 5 min, the fresh gas flow rate was reduced to $1\,l{\cdot}min^{-1}$. A semiclosed-circle system with a soda lime absorbent (Drägersorb 800; Dräger, Lübeck, Germany) was used to absorb CO_2. The CO_2 absorbent was changed before the administration of anesthetics to each patient. The anesthesia machine was a Narcomed IIB (North American Dräger, Telford, PA, USA). A radial arterial catheter was inserted to monitor arterial blood pressure and to obtain blood samples for analysis of arterial blood gases and serum inorganic fluoride concentrations. The lungs were ventilated mechanically with a tidal volume of $8–10\,ml{\cdot}kg^{-1}$, and the ventilatory rate was adjusted to maintain an end-tidal CO_2 partial pressure of 35–40 mmHg. End-tidal concentrations of sevoflurane were analyzed with a Capnomac Ultima gas analyzer (Capnomac; Datex, Helsinki, Finland) that was calibrated immediately before each study. The anesthetic concentration was adjusted by the anesthesiologist to maintain the mean arterial blood pressure within ±20% of baseline. No adjunct anesthetics or vasoactive drugs were used. A temperature probe (model DT-300; Intermedical, Tokyo, Japan) was inserted into the center of the upper absorbent canister, and the soda lime temperature was recorded at 5-min intervals. After postoperative X-ray films of the surgical site were obtained, anesthetic administration was discontinued and the fresh gas inflow rate was changed to $6\,l{\cdot}min^{-1}$ of oxygen. After the patient opened his eyes and took a deep breath on verbal command, the endotracheal tube was removed.

Lactated Ringer's solution was administered at 5–$6\,ml{\cdot}kg^{-1}{\cdot}h^{-1}$ during anesthesia and at $2\,ml{\cdot}kg^{-1}{\cdot}h^{-1}$ for 16 h after cessation of anesthetic exposure. Clinical laboratory studies of parameters such as serum uric acid, blood urea nitrogen (BUN), and serum creatinine concentrations were performed immediately before anesthesia and repeated 1, 2, 3, 5, and 7 days after the initiation of anesthesia. Urine samples (24 h) were collected before anesthesia and for at least 7 days after anesthesia. These samples were used for the measurement of the urinary excretion of total protein, albumin, β_2-microglobulin, glucose, *N*-acetyl-β-glucosaminidase (NAG), and creatinine. Urine collection after anesthesia began at the end of anesthesia and continued for each 24-h period from 0 to 168 h.

Gas samples were obtained from the inspiratory limbs of the anesthetic circuit distal to the one-way valves via a capped stopcock port, using gas-tight glass syringes for compound A analysis. Inspiratory limb gas samples were obtained from the inspiratory limb every 1 h after intubation and at the end of anesthesia, using a gas-tight locking syringe. The gas was injected into a gas chromatograph (GC-14A; Shimadzu, Kyoto, Japan). A glass column with a length of 5 m and an internal diameter of 3 mm packed with 20% dioctyl phthalate on a Chromosorb WAW (GL Science, Tokyo, Japan) 80/100 mesh was maintained at 110°C in the gas chromatogram. The injection port was maintained at 130°C. A carrier stream of nitrogen, flowing at $30\,ml{\cdot}min^{-1}$, was delivered through the column to a hydrogen flame ionization detector. The gas chromatograph was calibrated by preparing standard calibration gases from stock solutions of compound A supplied by Maruishi Pharmaceutical (Osaka, Japan).

Routine laboratory tests such as BUN, urinary protein, albumin, β_2-microglobulin, glucose, and NAG concentrations, were measured at the Clinical Laboratories of SDFCH. The measurements were performed in a single-blinded manner. Urinary protein and glucose concentrations were measured with a Hitachi 7170 Auto Analyzer (Hitachi, Tokyo, Japan). Urinary albumin concentration was measured with a Nephrometer Analyzer II (Behring, Mrabury, Germany). Urinary β_2-microglobulin was measured by radioimmunoassay (β_2-Micro · RIABEARS; Dainabot, Tokyo, Japan). Urinary NAG activity (24 h) was determined colorimetrically using a commercially available method (Shionogi, Osaka, Japan). Urinary excretion of NAG was expressed relative to creatinine concentrations.

The anesthetic dose was calculated as the product of end-tidal sevoflurane concentration (expressed as minimum alveolar concentration [MAC], where 1 MAC = 2.4%) [15] and time, according to the equation [MAC-h = (end-tidal concentration %/2.4) × 1/12 h]. Values taken at 5-min intervals were summed over the period of exposure to obtain the total delivered sevoflurane dose. Compound A exposure was calculated from the area under the curve (AUC) of compound A concentration versus time, using the trapezoid rule.

Values are expressed as means ± SD. Inter- and intragroup comparisons of laboratory data were performed using two-way repeated measures analysis of variance. Patient demographic data, and maximum and average excretion data were analyzed by Student's *t*-test or Welch's test. For variables that were not normally distributed (e.g., urinary protein, albumin, β_2-microgloblin, and glucose), Student's *t*-test or Welch's test was conducted using log-transformed data. Differences were considered statistically significant if the *P* value was less than 0.05.

Results

There were no differences between the groups in age, height, body weight, duration of anesthesia and surgery, MAC-h, the individual peak and mean compound A concentration, and compound A inspired AUC (Table 1). The two groups did not differ in clinical laboratory baseline values, and no abnormal changes in values in renal function studies were noted during the study period; neither elevated BUN and serum creatinine nor decreased creatinine clearances were observed in any patient (Table 2).

Urinary excretion of total protein was significantly increased after anesthesia in both groups compared with values obtained before anesthesia (Fig. 1), but the amounts did not differ between the groups. There were no significant differences in either the maximum or the average values for urinary excretion of total protein after anesthesia between the amikacin and control groups (Figs. 2A and 3A).

Changes over time in the urinary excretion of albumin, β_2-microglobulin, glucose, and NAG were similar to the changes in the urinary excretion of total protein. There were no significant differences between the two groups in either the maximum or average values for the urinary excretion of these biochemical markers (Figs. 2, 3).

Discussion

The present study demonstrated that there were no significant differences between our two groups in either the maximum or the average values for the urinary excretion of biochemical markers after anesthesia. In this study, we compared the urinary excretion of several biochemical markers in patients given cefotiam with the urinary excretion of these markers in patients given cefotiam plus amikacin. The amikacin group received amikacin so that the effects of amikacin on renal function could be investigated. Cefotiam was also adminis-

Table 1. Patient demographics

	Amikacin (n = 18)	Control (n = 19)
Age (years)	24.4 ± 4.2	26.3 ± 5.7
Height (cm)	170.8 ± 6.7	169.0 ± 8.4
Weight (kg)	68.7 ± 9.4	69.8 ± 10.6
Duration of surgery (min)	239.2 ± 81.8	230.9 ± 105.2
Duration of anesthesia (min)	314.7 ± 81.8	307.9 ± 98.3
Total anesthetic dose (MAC-h)	7.0 ± 2.3	7.0 ± 2.4
Blood loss (ml)	59.5 ± 68.3	63.9 ± 99.4
Compound A concentration		
Peak compound A concentration (ppm)	39.4 ± 3.2	40.8 ± 10.5
Mean compound A concentration (ppm)	27.2 ± 8.7	27.1 ± 7.8
Compound A inspired AUC (ppm-h)	144.5 ± 56.1	136.2 ± 54.1

Values are mean ± SD

Table 2. Perioperative blood urea nitrogen (BUN), serum creatinine concentration, and creatinine clearance

	BUN ($mg \cdot dl^{-1}$)		Serum creatinine ($mg \cdot dl^{-1}$)		Creatinine clearance ($ml \cdot min^{-1}$)	
	Amikacin	Control	Amikacin	Control	Amikacin	Control
Preoperative	14 ± 3	15 ± 3	0.9 ± 0.1	0.9 ± 0.1	102 ± 27	103 ± 19
1 Day postoperative	10 ± 3**	10 ± 3**	0.9 ± 0.1	0.9 ± 0.1	126 ± 29*	130 ± 42*
3 Day postoperative	11 ± 3**	10 ± 3**	0.9 ± 0.1	0.9 ± 0.1	112 ± 36	105 ± 21
5 Day postoperative	14 ± 3	14 ± 3	0.9 ± 0.1	0.9 ± 0.2	116 ± 37	106 ± 29
7 Day postoperative	14 ± 3	15 ± 4	0.9 ± 0.1	0.9 ± 0.1	101 ± 27	102 ± 24

Difference from control *$P < 0.05$; **$P < 0.01$
Values are means ± SD

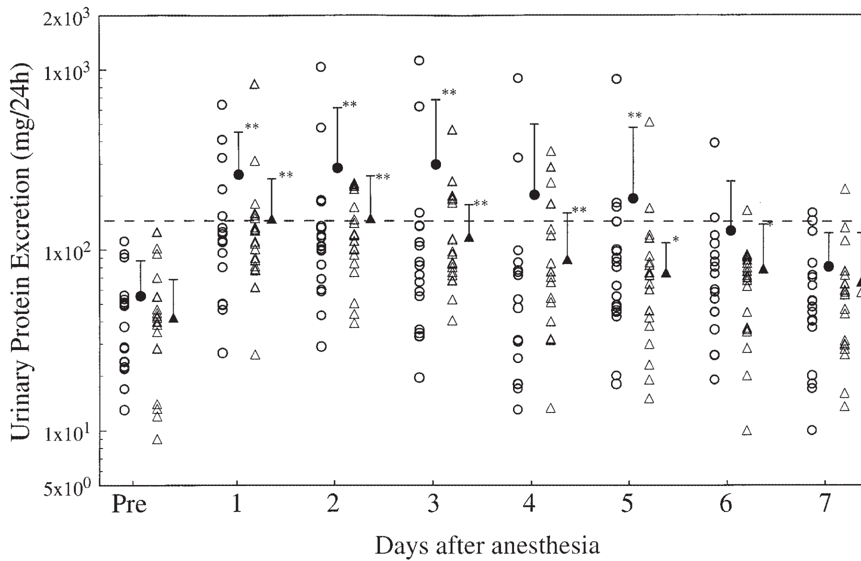

Fig. 1. Changes over time in urinary excretion of total protein in the two groups. Individual (*open symbols*) and mean ± SD values (*closed symbols*) are shown. Note the logarithmic scale used in this graph. The *dotted line* represents the upper limit of the reference range ($150\,\mathrm{mg \cdot 24\,h^{-1}}$). $*P < 0.05$ compared with each preoperative value; $**P < 0.01$ compared with each preoperative value. *Circles*, Amikacin; *triangles*, control

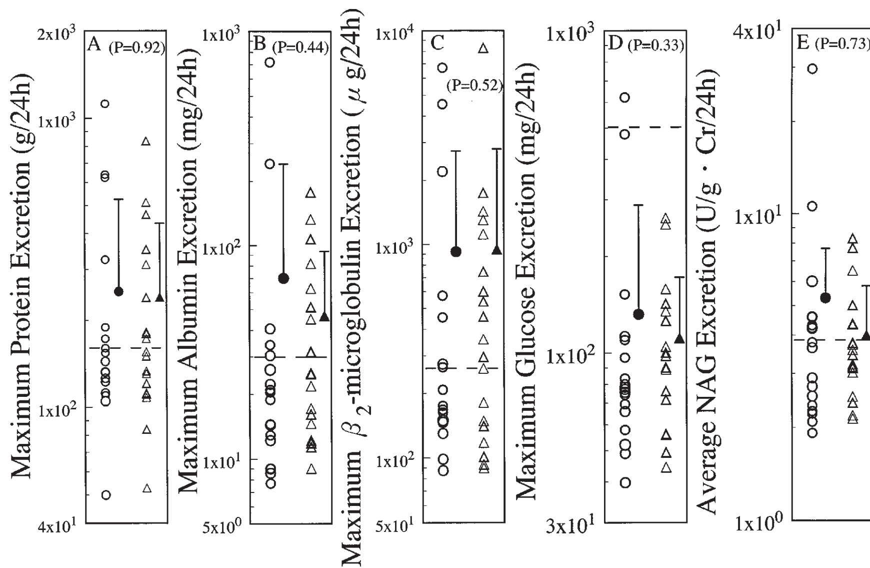

Fig. 2A–E. Maximum values of biochemical markers after anesthesia. Individual (*open symbols*) and mean + SD values (*closed symbols*) are shown. Note the logarithmic scale used in this graph. Each *dotted line* represents the upper limit of the reference range. There were no significant differences in the maximum urinary excretion of protein (**A**), albumin (**B**), β_2-microglobulin (**C**), glucose (**D**), and *N*-acetyl-β-glucosaminidase (*NAG*) (**E**) after anesthesia between the amikacin group and the control groups. Cr, creatinine

tered to the amikacin group for prophylaxis, however, because amikacin is not effective for gram-positive infections.

The renal tubule is the site of compound A nephrotoxicity in rats; in particular, the tubules in the outer strip of the outer medullary layer (corticomedullary junction) [3,4]. Aminoglycosides also injure the proximal tubules in rats and humans [11,16]. The combined use of aminoglycosides with a known nephrotoxin that causes proximal tubule injury, such as cisplatin, can enhance nephrotoxicity [11]. The combination of aminoglycosides and cephalosporin antibiotics does not seem to enhance nephrotoxicity, although this matter is controversial [11,16]. In 1970, Kuzucu [12] demonstrated that tetracycline intensified the nephrotoxicity produced by methoxyflurane administration in humans. Mazze and Cousins [13] and Barr et al. [17] reported the combined nephrotoxicity of gentamicin and methoxyflurane in rats and humans, respectively. Motuz et al. [14] reported further increases in the urinary excretion of alanine aminopeptidase (AAP), a brush-border enzyme, associated with enflurane after aminoglycoside administration. In contrast, Fish et al. [18] reported that anesthesia with either enflurane or halothane in rats with chronic renal impairment treated with gentamicin did not result in additional renal damage. In contrast to the results of Motuz et al. [14], there was no synergic effect on the increase of urinary biochemical markers in

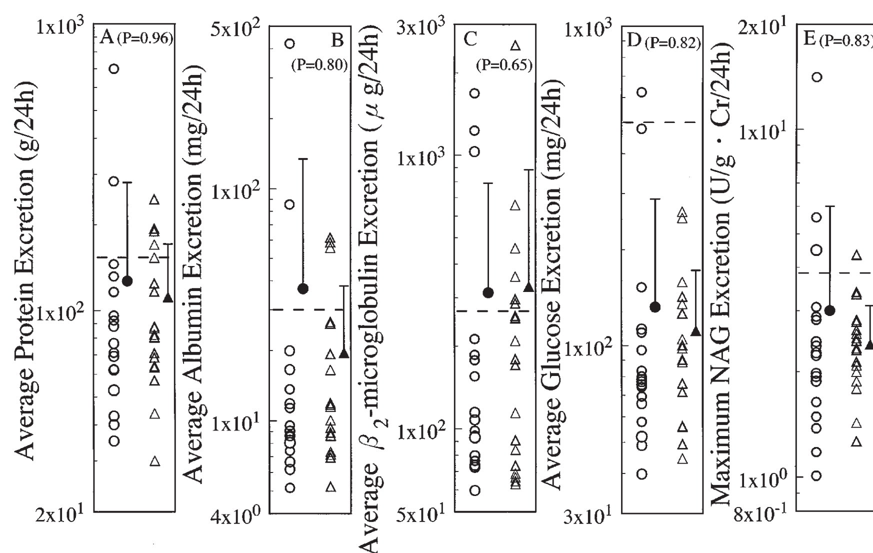

Fig. 3A–E. Mean values of biochemical markers during 7 days after anesthesia. Individual (*open symbols*) and mean + SD values (*closed symbols*) are shown. Note the logarithmic scale used in this graph. Each *dotted line* represents the upper limit of the reference range. There were no significant differences in the maximum urinary excretion of protein (**A**), albumin (**B**), β_2-microglobulin (**C**), glucose (**D**), and NAG (**E**) after anesthesia between the amikacin group and the control group. Cr, creatine

the present study. This difference may have been caused by differences in the type of aminoglycoside examined, the patients ages, the low dose of amikacin in the present study, or the compound A-inspired AUC. In the present study, young healthy patients (mean age, 26 years) received amikacin as the aminoglycoside. In contrast, the patients in the study by Motuz et al. [14] (mean age, 63 years) received either gentamicin or tobramycin as the aminoglycoside. Age over 60 years is a clinical risk factor for aminoglycoside nephrotoxicity [11,16]. Amikacin is less nephrotoxic than gentamicin [19]. The dose of amikacin used in the present study was approximately $6\,mg \cdot kg^{-1} \cdot day^{-1}$: this dose was lower than that used in the study by Mondorf et al. [20], which reported increases in AAP in volunteers given $10\,mg \cdot kg^{-1} \cdot day^{-1}$. Furthermore, the compound A-inspired AUCs in the present study were relatively small, with the values both being below 150 ppm-h (137 ppm-h and 144 ppm-h, respectively), in both groups. Compound A nephrotoxicity in rats is dose dependent [3,4], and the dose-dependent effect may also be applicable to humans. Eger et al. [21] have contended that the threshold for compound A nephrotoxicity in humans is 150 ppm-h. Therefore, it is possible that larger doses of amikacin with more prolonged compound A inspiration than that used in the present study might cause renal damage.

The duration of amikacin treatment in the present study was relatively short. The percentage of patients who experience nephrotoxicity increases with duration of therapy [11]. Mondorf et al. [20], however, reported increases in AAP in volunteers given amikacin for only 3 days. The investigation by Kosek et al. [22] demonstrated the rapid formation of lysosomal cytosegresomes in Fischer 344 rats given gentamicin ($1\,mg \cdot kg^{-1} \cdot day^{-1}$) for 2 days. Furthermore, synergic increases were induced by aminoglycosides and enflurane in the urinary excretion of AAP on day 2 after anesthesia in the study by Motuz et al. [14]. Thus, the duration of treatment in the present study was probably not a factor.

The timing of administration of amikacin may also have affected the results. In the present study, amikacin administration began on the day of compound A inspiration. Barr et al. [17] reported that rats receiving gentamicin beginning on the day of methoxyflurane administration had less nephrotoxicity than rats given gentamicin prior to methoxyflurane administration. If the patients in the present study had been given amikacin prior to anesthesia, the results may have been different.

In conclusion, amikacin and low-flow sevoflurane anesthesia had no synergic effect on nephrotoxicity in this study. The duration of amikacin treatment was short, however, and the doses of amikacin and compound A were relatively low. Further study with substantially higher doses of amikacin and compound A is required to establish the safety of low-flow sevoflurane with aminoglycoside definitively.

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