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Biological Indices of Kidney Involvement in Personnel Exposed to Sevoflurane in Surgical Areas

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Background *Fluoride, a main metabolite, and one degradation product of sevoflurane (SEV), called Compound A, are known to cause kidney effects in experimental animals. Other than in volunteers and patients, no research is available on exposed workers. The possible effects on the kidney in workers exposed in surgical areas were studied.*

Methods *Subjects exposed to SEV and nitrous oxide (N_2O) in surgical areas ($N = 61$) using open ($N = 25$) or semi-closed ($N = 36$) circuits were submitted to biological monitoring. The same biological indices were determined in 43 controls also. Sevoflurane (SEVU), nitrous oxide (N_2OU), total urinary proteins (TUP), N-acetyl-β-D-glucosaminidase (NAGU), and glutamine synthetase (GSU) were measured in urine.*

Results *The mean values of environmental exposure were 31.3 ppm (range 0.9–111.6 ppm) for N_2O and 0.28 ppm (range 0–1.88 ppm) for SEV. Exposed subjects had significantly higher excretion of TUP; a higher, not significant, excretion of GSU was also observed in subjects using open circuits. A significant correlation was found in all exposed subjects between NAGU and SEVU ($r = 0.303$, $P < 0.05$), GSU and N_2OU ($r = 0.382$, $P < 0.01$) and, especially, GSU and SEVU ($r = 0.650$, $P < 0.001$). These correlations appeared to be influenced by the use of open circuits; infact, NAGU was well correlated to N_2OU ($r = 0.770$, $P < 0.001$) and SEVU ($r = 0.863$, $P < 0.001$); GSU to N_2OU ($r = 0.468$, $P < 0.05$) and SEVU ($r = 0.735$, $P < 0.001$).*

Conclusions *Results show that no relevant effect on the kidney is present for the levels of exposure studied. Nevertheless, correlation between dose and response urinary indices supports that SEV, other than N_2O, may influence kidney function, especially when open circuits are used.* Am. J. Ind. Med. 44:474–480, 2003. © *2003 Wiley-Liss, Inc.*

KEY WORDS: sevoflurane; nitrous oxide; kidney involvement; urinary proteins; urinary enzymes

INTRODUCTION

The introduction of sevoflurane (SEV) in the practice of anesthesia by inhalation is recent (only since 1997 in Italy). SEV has low solubility in blood, owing to a low blood-gas repartition coefficient, with higher alveolar concentrations during anesthesia induction, better control of alveolar concentrations during the maintenance of anesthesia, and

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faster reduction of alveolar concentrations during the elimination phase. The anesthetic is metabolized in the liver by means of cytochrome P-450 2E1 to form equimolar concentrations of hexafluoroisopropanol (HFIP) and fluoride (F) ions; the metabolite HFIP is stable, and is rapidly conjugated with glucuronic acid and excreted in the urine [Kharasch et al., 1995]. Several studies have evaluated the possible interference of SEV with the organism: effects on central nervous system with electroencephalographic alterations [Kameyama, 1994], on reproductive function with spontaneous abortion [Pihlainen and Ojanpera, 1998], or the possibility of inducing malignant hyperthermia [Patel and Goa, 1996] are described. Much interest has been aroused as regards renal effects. There are two possible causes of renal damage: F^- ion formation [Higuchi et al., 1995] and, during anesthesia in semi-closed circuit, the formation of fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether called Compound A [Iyer and Anders, 1997].

Compound A derives from degradation of SEV in the presence of a soda-lime medium used to absorb carbon dioxide in semi-closed circuit; a second product (Compound B) also forms [Morio et al., 1992]. The formation of Compound A is only possible in patients during anesthesia, and does not seem to be a problem for personnel in surgical areas.

Generally, studies conducted in patients do not demonstrate significant renal effects either by F or Compound A. However, Compound A is well known to induce nephrotoxicity in experimental animals at the level of the proximal tubule [Jin et al., 1995; Iyer et al., 1997].

At this moment, no study is available on the renal effects caused by SEV in exposed subjects working in surgical areas. In the present research, the possible effects on the kidney were studied in personnel of various surgical areas usually exposed to SEV and nitrous oxide (N_2O) during anesthesia.

Urinary biochemical parameters of renal effects were measured and SEV and N_2O in urine were determined. SEV was used in both open and semi-closed circuits; the differences between these two types of SEV use were also considered.

MATERIALS AND METHODS

Sixty-one subjects employed in 12 operating areas as surgeons, assistant surgeons, anesthetists, and nurses were monitored in order to evaluate personal exposure to anesthetic gases. The investigation involved orthopedics, urology, gynecology, otorinolaryngology, and vascular and general surgery. Subjects were exposed to N_2O and SEV with open (high gas flow, about 6–7 l/min; $N = 25$) or semi-closed circuit (about 2 l/min, with addition of anesthetic gas when blood concentration decreases below the operative conditions; $N = 36$).

Forty-three subjects employed in hospital areas but not exposed to anesthetic gases, paired for age, sex, socioeconomic habit and status, and body mass index (BMI) were used as a control group. The characteristics of all subjects (exposed and controls) are listed in Table I.

Exposed subjects were monitored throughout the surgical session by means of Radiello® [Cocheo et al., 1996] passive samplers; the samplers were then eluted in a water/methanol (60/40, v/v) mixture, and the anesthetics were determined by chromatographic methods and mass spectrometry (analytical conditions were for SEV: ion mass monitored = 31, 69, 131, and 181; dwell time = 0.2 s; multiplier = 300 V; for N_2O: ion mass monitored = 44; dwell time = 0.2 s; multiplier = 300 V)

Spot urine samples were obtained at the end of operating sessions to assay N_2O (N_2OU) by means of head-space gas-chromatographic analysis with an ECD detector (autosystem XL) and SEV (SEVU) by means of gas-chromatography and mass-spectrometry. Analytical conditions of mass-spectrometry were: ion mass monitored = 31, 69, 131, and 181; dwell time = 0.2 s; multiplier = 400 V. In addition, total urinary proteins (TUP) according to Pesce and Strande [1973], N-acetyl-β-D-glucosaminidase (NAGU, E.C. 3.2.1.29) according to Lockwood and Bosmann [1979], using 4-nitrophenyl-N-acetyl-β-D-glucosaminide (Fluka, Buchs, Switzerland) as substrate, and glutamine synthetase (GSU, E.C. 6.3.1.2) according to Trevisan et al. [1999], using L-glutamic acid (Sigma Chemical Co, St.

TABLE I. Differences in Sex, Age, and BMI of Surgeons, Assistant Surgeons, Anesthetists, and Nurses Exposed to Sevoflurane and Control Subjects*

	Exposed			Controls		
	Total	Males	Females	Total	Males	Females
Number	61	31	30	43	21	22
Age	39.3 ± 8.7	42.8 ± 8.5	35.7 ± 7.4	39.6 ± 10.8	45.7 ± 10.0	33.8 ± 8.1
BMI	23.3 ± 3.2	24.5 ± 2.3	22.1 ± 3.6	22.7 ± 3.1	24.5 ± 2.4	20.9 ± 2.6

*Results are presented as means ± standard deviations.

Louis, MO) as substrate were also determined. All urinary values were referred to millimoles of creatinine, determined with a commercial kit (Boehringer, Mannheim, Germany).

Apparatus

Instruments for anesthetic analysis were from Perkin-Elmer (Norwalk, CT, USA); proteins, enzymes, and creatinine in urine were measured on a Perkin-Elmer lambda 5 model UV-visible spectrophotometer.

Statistical evaluation of results was performed by variance analysis and correlation coefficient r.

RESULTS

The mean values of environmental pollution in all operating areas were 31.3 ppm (range 0.87–111.61 ppm) for N_2O and 0.28 ppm (range 0–1.88 ppm) for SEV. If an open circuit was used, mean values for N_2O were 34.9 ppm (range 0.87–99.45 ppm) and for SEV 0.41 ppm (range 0.02–1.88 ppm); on the contrary, semi-closed-circuit users showed a mean exposure level of 28.3 ppm (range 0.88–111.61 ppm) for N_2O, and 0.18 ppm (range 0–1.4 ppm) for SEV. These values exceeded the National Institute of Occupational Safety and Health [NIOSH, 1977] recommended limits for N_2O (25 ppm), and were below the limit of 0.5 ppm for fluorinated anesthetics in the presence of N_2O. Nevertheless, the mean value of N_2O is below the ACGIH [2002] TLVs (50 ppm) and the Italian limit established by a circular from Italian Ministry of Health (50 ppm). There are no environmental limits for SEV.

Table II lists the mean values of urinary indices of dose and effect. The exposed group showed a slight but significant increase in TUP with respect to controls, although all the values were in the normal range. Exposed subjects using semi-closed circuits during operating sessions showed significant lower excretion of SEVU than in open circuit; N_2OU excretion also appeared to be lower, but without reaching significance. Subjects using open circuit also showed higher but not significant excretion of GSU than semi-closed circuit users and controls.

More interesting were the correlations among dose-response indices. In all exposed subjects (Fig. 1), low but significant correlations were observed between NAGU and SEVU ($r = 0.303$, $P < 0.05$), GSU and N_2OU ($r = 0.382$, $P < 0.01$), and, especially, GSU and SEVU ($r = 0.650$, $P < 0.001$). These correlations were influenced by open circuit use, where the exposure to N_2O and, particularly, to SEV was higher than semi-closed circuit. In fact (Fig. 2), in subjects using open circuit, NAGU was well correlated with N_2OU ($r = 0.770$, $P < 0.001$) and SEVU ($r = 0.863$, $P < 0.001$), GSU to N_2OU ($r = 0.468$, $P < 0.05$), and SEVU ($r = 0.735$, $P < 0.001$). No significant correlation was observed among urinary indices in semi-closed circuit users. In contrast with significant differences in TUP excretion, no correlation was found between this index of effect and indices of dose.

Lastly, no significant correlation between age, length of exposure, or urinary indices of effects was found.

DISCUSSION

The present research aimed to study possible renal effects in subjects exposed to SEV during surgical operations. Personnel were exposed to quite low concentrations of N_2O (average 31.3 ppm); in fact they are below the ACGIH [2002] TLVs, even if they exceeded the, in our opinion overprotective, [NIOSH, 1977] limit of 25 ppm. In our study, the mean values of SEV are 0.28 ppm, below the NIOSH limit of 0.5 ppm for fluorinated anesthetics in the presence of N_2O. Nevertheless, this limit was fixed many years ago for

TABLE II. Urinary Values of Controls and Workers Exposed to Sevoflurane (Subdivided Into Open or Semi-Closed Circuits)*

			Exposed workers		
		Controls	Total	Open	Semi-closed
Number		43	61	25	36
N_2OU	μg	n.d.	3.52 ± 4.10	4.21 ± 4.92	3.04 ± 3.42
SEVU	μg	n.d.	0.23 ± 0.62	0.42 ± 0.91[b]	0.10 ± 0.19
TUP	mg	3.6 ± 2.9	6.8 ± 7.0[a]	6.8 ± 4.3[a]	6.9 ± 8.5[a]
NAGU	μmol	0.40 ± 0.15	0.30 ± 0.19	024 ± 0.14	0.34 ± 0.20
GSU	μmol	0.75 ± 0.45	0.80 ± 0.69	0.92 ± 0.95	0.72 ± 0.44

*Results are presented as means ± standard deviations. Values refer to millimoles of creatinine.
n.d., not detectable.
[a] $P < 0.05$ or more with respect to controls.
[b] $P < 0.05$ or more between open and semi-closed circuits.

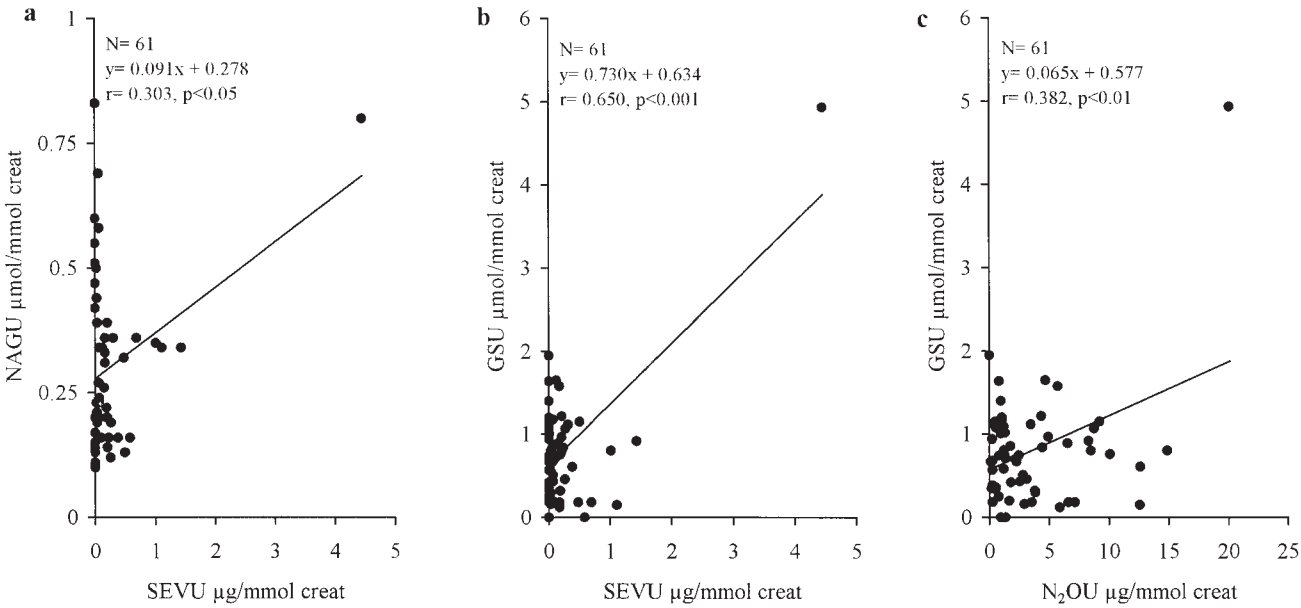

FIGURE 1. Correlations among urinary indices of dose and effect in all exposed subjects; (**a**) correlation between SEVU and NAGU, (**b**) between SEVU and GSU, and (**c**) between N_2OU and GSU.

different gases than SEV, such as halothane and enflurane [Berry, 1999].

Several experimental and clinical studies have been performed to define the renal effects of SEV, but only a few, older studies describe some renal effects induced by N_2O. In short, N_2O reduces the antidiuretic effects caused by morphine [Bidwai et al., 1975] or fentanyl [Bidwai et al., 1976] and the natrium/potassium ratio in urine, creatinine clearance and urinary flow, and increases urinary osmolality [Nuutinen, 1976]. Instead, the extensive literature on possible nephrotoxicity caused by SEV prevalently discusses effects on animals, volunteers or patients of the degradation product of the anesthetic (Compound A) after soda-lime crossing. Numerous experimental researches demonstrate selective necrosis of the proximal tubule [Nuutinen, 1976; Jin et al., 1995, 1996; Kandel et al., 1995; Kharasch et al., 1997, 1998]. Effects appeared to be related to cysteine-conjugate β-lyase-dependent bioactivation [Iyer and Anders, 1997]. Kharasch et al. [2001] recently reported that low-flow SEV is safe in patients, even with long exposures. These results agree with those of other authors [Bito and Ikeda, 1994; Conzen et al., 1995; DeSouza and Gold, 1997; Getz and Malan, 2001].

Conversely, conflicting conclusions are reported in studies performed on patients and volunteers: transient injury to glomeruli (with albuminuria), and in proximal (with glycosuria and increase in α-glutathione-S-transferase in urine) and distal tubules (with increase of π-glutathione-S-transferase in urine) was observed [Eger et al., 1997a]; these effects appeared to increase with duration of exposure [Eger et al., 1997b]. Patients treated with low-flow SEV showed urinary increases in TUP, NAG, and β_2-microglobulin [Higuchi et al., 1995], whereas probenecid prevented these effects. Higuchi et al. [1995] also observed a reduction in the maximum capability to concentrate urine and an increase in urinary NAG; these data were later supported [Higuchi et al., 1998].

Surprisingly, no studies are available on the renal effects caused by SEV in subjects working in surgical areas.

SEV is metabolized by liver cytochrome P-450 2E1 to form equimolar concentrations of HFIP and F^- ions [Kharasch et al., 1995]. It is known that fluoride causes renal toxicity in experimental models, inducing dose-dependent cytotoxicity in cultured human proximal tubular cells [Zager and Iwata, 1997] and serious disorders in the pars recta of the proximal tubule with increased urinary excretion of α-glutathione-S-transferase [Usuda et al., 1998].

The results presented here show that not only SEV but also N_2O negatively influences the urinary indices of effects. In our laboratory, a test battery to study the effects of xenobiotics on the kidney is generally used. NAG, a lysosomal enzyme prevalently distributed along the pars convoluta but also present in the pars recta in rat [Le Hir et al., 1979] and rabbit [Bourbouze et al., 1984], but prevalently in the pars recta in humans [Schmid et al., 1986], is largely used to detect damage of the proximal tubule caused by xenobiotics such as solvents [Brogren et al., 1986], metals [Meyer et al., 1984; Chia et al., 1994; Usuda et al., 1998], and silica [Ng et al., 1992]. In addition, the detection in urine of GS, a mitochondrial enzyme exclusively located in the early and late portions of the S_3 segment [Burch et al., 1978], was recently suggested as a marker of S_3 segment-specific

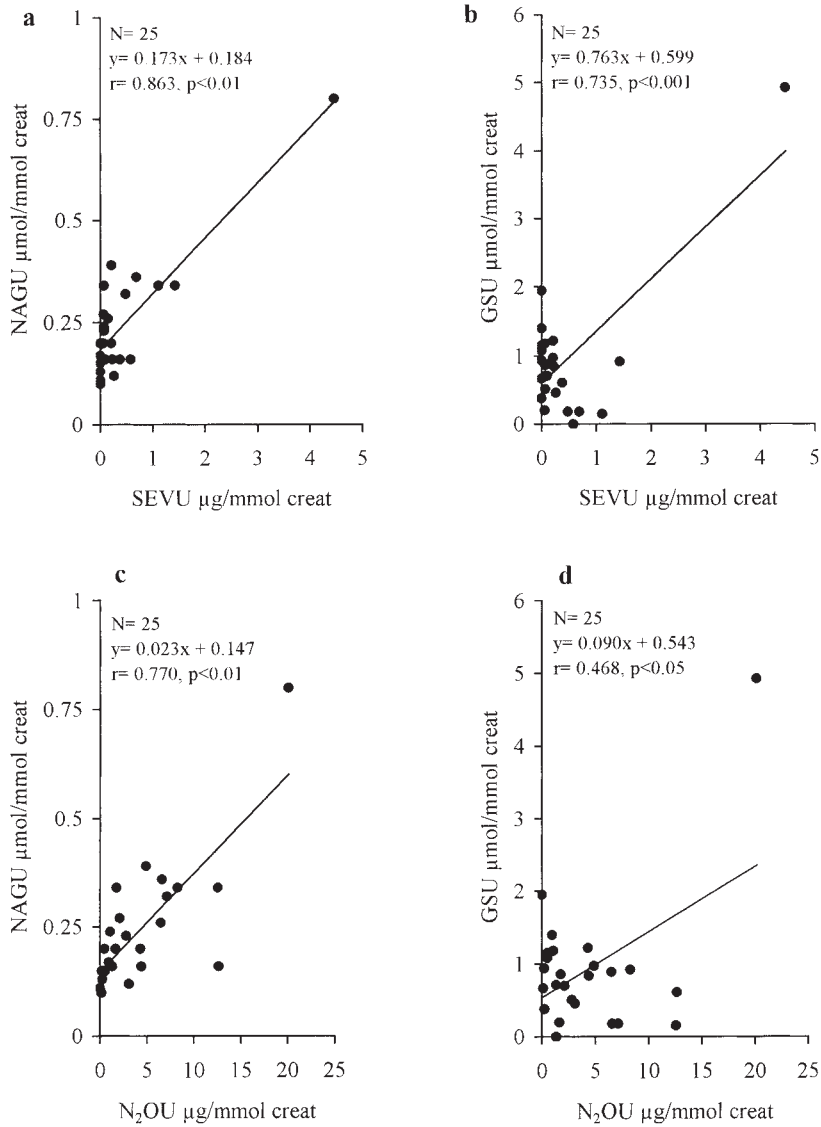

FIGURE 2. Correlations among urinary indices of dose and effect in exposed subjects using SEV in open circuit; (**a**) correlation between SEVU and NAGU, (**b**) between SEVU and GSU, (**c**) between N_2OU and NAGU, and (**d**) between N_2OU and GSU.

damage in rats treated with hexachloro-1:3-butadiene [Trevisan et al., 1999]. Lastly, TUP values are determined as general and not specific indices of kidney involvement.

In our study, even if all the values were in the normal range, a slight but significant difference between exposed and control group was observed only for TUP excretion. Study of the correlations in surgical area personnel between dose and effect urinary indices shows that GSU and NAGU are good indices of renal effect in subjects exposed to SEV. The evidence that only subjects using open circuits present these effects supports the role of SEV and its metabolite fluoride in kidney involvement, excluding effects caused by Compound A. Interestingly, N_2O also affects urinary indices in open but not in semi-closed circuit users. In addition, SEV appears to produce the prevalent effects on the pars recta of the proximal tubule, according to the evidence that GS is an enzyme exclusively located in the S_3 segment [Burch et al., 1978], effects mediated by F that are known to cause damage in this tubular segment [Usuda et al., 1998]. This fact is also supported by the significant correlation with NAG, an enzyme distributed along the proximal tubule, but in humans prevalently in the S_3 segment [Schmid et al., 1986].

In conclusion, results show that no relevant effect on the kidney is present for subjects exposed to concentrations of anesthetic gases below limit values such as 50 ppm adopted by ACGIH for N_2O and 0.5 ppm suggested by NIOSH for fluorinated anesthetics in presence of N_2O. Nevertheless, the significant correlation between dose and response urinary

indices supports that SEV may influence the kidney function of personnel exposed to SEV when open circuits are used for anesthesia induction and maintenance. In addition, co-exposure with N_2O may play a role in the expression of these effects. Lastly, the use of low flow anesthesia suggests the possibility to prevent slight kidney effects. These are preliminary data and the suggestions of correlation with kidney effect needs further study.

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