POSTOPERATIVE RENAL AND HEPATIC FUNCTIONS AFTER LOW FLOW SEVOFLURANE COMPARED WITH ISOFLURANE ANESTHESIA

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Abstract

Sevoflurane degradation by carbon dioxide absorbents during low-flow anesthesia forms compound A, which causes nephrotoxicity in rats. This study was done to evaluate post operative renal and hepatic functions after patients were administered Sevoflurane under conditions designed to generate high concentration of compound A. Consenting forty patients ASA physical status I, II with normal pre operative renal and hepatic function undergoing anesthesia for elective surgery with planned duration exceeding 2 h. They were randomized to receive Sevoflurane (n=20) or Isoflurane (n=20) in oxygen. Total gas flow was 1L/min. opioid doses were minimized and barium hydroxide lime was used to maximize anesthetic degradation. Blood and urine were obtained before and 1, 2 and 3 days after anesthesia for laboratory evaluation. Sevoflurane and Isoflurane groups were similar with respect to age, weights sex, ASA status and anesthetic duration (2-4h). There was no significant difference between anesthetic groups in postoperative serum creatinine, BUN, and urinary excretion of protein. Post operative alanine and aspartate amino transferase concentration were not different between the anesthetic groups. It is concluded that renal tubular and hepatic effects of low-flow Sevoflurane and Isoflurane were similar as assessed using both conventional measures of renal and hepatic functions. Moderate duration of low-flow Sevoflurane anesthesia, during which compound A formation occurs appears to be as safe as low-flow Isoflurane anesthesia.
Introduction

Sevoflurane is a safe and versatile inhalational anesthetic compared with currently available agents. Sevoflurane is useful in adult and children for both induction and maintenance of anesthesia in inpatient and outpatient surgery. Of all currently used anesthetics, the physical, pharmacodynamic, and pharmacokinetics properties of sevoflurane come closest to that of ideal anesthetic. These characteristics include inherent stability, low flammability, non-pungent odor, lack of irritation to airway passages, low blood-gas solubility coefficient of 0.6 -0.69 (Strum and Egar 1987) allowing rapid induction and emergence from anesthesia, minimal cardiovascular and respiratory side effects, minimal end-organ effects and minimal effect on cerebral blood flow. However a few investigators Egar et al. 1997 and Higuchi et al., 1998 continued to question its potential of causing renal toxicity for two reasons. first, because it reacts with carbon dioxide absorbents to produce the vinyl ether, CH₂F-O-CC=CF₂ (CF₃), known as compound A, which is responsible for nephrotoxicity in rats (Gonsowsk et al., 1994), and second, because it is biotransformed to inorganic fluoride. Desflurane, enflurane and isoflurane are not known to undergo degradation to nephrotoxic difluorovinyl products.

Compound A, nephrotoxicity is characterized histologically as corticomedullary tubular necrosis localised to the proximal tubules. The biochemical manifestations, include elevation in serum blood urea nitrogen (BUN) and creatinine, glucosuria and proteinuria, and increased urinary excretion of N-acetyl-B-D-glucosaminidase (NAG) and alpha glutathione-S-transferase (αGST), a site specific tubular cell enzymes (Jin et al., 1995) and (Morio et al., 1992). However, Kharasch et al 1997 suggested that the mechanism of compound A nephrotoxicity in rats appears to involve metabolism to glutathione and cysteine conjugates, and their subsequent renal uptake and metabolism by pathways that are different in rats and human.

Aim of the work

The aim of this work is to com-
pare the postoperative effects of low flow sevoflurane and isoflurane on renal and hepatic function in patients (n=40) undergoing elective surgery of moderate duration (2-4) as evidenced by postoperative changes in serum creatinine and blood urea nitrogen (BUN) concentrations, as well as urinary excretion of protein as fine indices of renal injury. Also postoperative alanine and aspartate amino transferase concentrations changes as indices of liver cell injury.

Patients and Methods

Forty American Society of Anesthesiologist (ASA) Physical status I, II patients undergoing anesthesia for elective surgery with planned duration exceeding 2 hour (2-4h) were subjected in this study. These patients had no history of hepatic diseases or renal insufficiency. Patients with history of previous known abnormality in serum creatinine (more than 1.5 mg/dL), aspartate amino transferase (AST) or alanine aminotransferase (ALT) concentrations were excluded. Patients undergoing renal or uretero genital surgery or procedures that compromise renal blood flow (cardiac and aortic surgery) were also excluded. All patients who were undergone general anesthesia within 2 weeks or who were treated with any experimental drug within 28 days of surgery were excluded. All female patients were tested and determined not to be pregnant or lactating. Every patient provided written informed consent.

The anesthetic protocol was designed to result in high compound A concentrations by using Fresh barium hydroxide lime (Baralyme) and by avoiding nitrous oxide use in anesthesia. Patients were randomly selected to receive low-flow sevoflurane anesthesia (low sevoflurane group n=20) or low flow isoflurane anesthesia (low-flow isoflurane group, n=20).

Fresh Baralyme was placed in the canister in both groups immediately before the anesthetics were placed.

Patients were premedicated with midazolam 0.05 mg/kg. Induction was thiopental. Fentanyl, 50-100 ug and 0.1 mg/kg vecuronium to facilitate tracheal intuba-
tion. After intubation anesthesia was maintained with sevolurane (0.8-2.5% end tidal) [sevoflurane group] or isoflurane (0.5-1.4% end tidal) [isoflurane group] in oxygen 100%. The fresh gas flow rate was set to 1L/min in both groups for the duration of the procedure. Nitrous oxide was not used in any patients. Electrocardiogram (ECG), non invasive automatic blood pressure monitor (Dinamap), end tidal CO₂ concentration, pulse oximetry and vital signs were monitored. Hemodynamic stability was maintained within 20% (±) of baseline by adjusting the inspired anesthetic concentration or with small doses of fentanyl. The lungs were ventilated mechanically with a tidal volume at 10-12 ml/kg with the ventilatory rate adjusted to maintain an end tidal CO₂ pressure of 30-40 mmHg. Reversal drug was administered as required at the end of operation.

Blood samples were obtained one day before operation, first, second and third days after anesthesia to measure BUN, creatinine concentrations as well as AST and ALT concentrations. Twenty-four hours urine samples were collected before anesthesia and for each 24 hours interval from 0 to 72 h after anesthesia to measure protein concentration.

Measured values were expressed as means ± standard deviation, statistical analysis of the data was carried out using one way analysis of variance, student-t- test and the Chi squared test as appropriate. A probability of less than 0.05 was considered to be statistically significant.

Results

Forty patients ASA physical status I, II were subjected in this study. 50% of the patients were maintained on low flow sevoflurane (sevoflurane group n=20) and the other 50% of the patients were maintained on low flow isoflurane (isoflurane group n=20).

Table (1) shown patient demographic data where there were no significant difference p>0.05) in age, body weight, sex. ASA physical status, duration of anesthesia and anesthetic exposure (MAC/ h).
Renal effects of low flow sevoflurane and isoflurane anesthesia were measured by serum BUN and creatinine concentration.

Blood urea nitrogen concentration decreased after anesthesia in both groups. This decrease was highly significant \( P<0.001 \) in comparison to the pre anesthesia values (table 3). However, there was no significant difference observed between the groups at any time after anesthesia (table 2). No patient had serum BUN concentration exceeding the upper limit of the reference range (20 mg/dl).

Serum creatinine concentration also decreased on post anesthesia day 3 significantly \( P<0.05 \) in the low-flow sevoflurane group but not significantly in the low-flow isoflurane group (table 5). However, there were no significant differences in serum creatinine concentration \( (P>0.05) \) between both groups (table 4). No patient had serum creatinine values higher than the upper limit of the normal range (1.3 mg/dl).

Figure (1) shown the twenty-four-hour protein excretion. There was no significant difference \( (P>0.05) \) between the patients who anesthetized with low-flow sevoflurane and isoflurane when measured post operatively in days 1, 2 and 3. \( (0-24 \text{ or } 24-48 \text{ or } 48-72h) \). Also there was no significant differences between post operative change compared to pre anesthesia values.

Table (6,7) shown the serum AST and ALT concentration. There was abnormal elevation of post operative AST and ALT value were observed in patients of both groups. But there was no significant differences between both groups \( (P>0.005) \) at 0, 24 and 72 hours after operation.
Table (1) Demographic data of sevoflurane and isoflurane groups.

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane group n=20 mean±SD (range)</th>
<th>Isoflurane group n=20 mean±SD (range)</th>
<th>P value</th>
<th>St sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patient</td>
<td>20</td>
<td>20</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>29.4±5.7 (24-40)</td>
<td>28.6±5.8 (24-42)</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/10</td>
<td>10/10</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>91±12 (25-100)</td>
<td>88±18 (50-125)</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>ASA status (I/II)</td>
<td>12/8</td>
<td>14/6</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of anesthesia (h)</td>
<td>3.4±1.6 (1.4-4.5)</td>
<td>3.9±1.8 (1.3-4.6)</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Exposure (Mac-h)</td>
<td>3.8±1.8 (0.9-6.5)</td>
<td>3.2±1.5 (0.6-5.9)</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

N.S no significance
P>0.05 non significant
P<0.05 significant
P<0.01 highly significant
P<0.001 very highly significant

Surgical procedure
- Laparotomy 5 5
- Laminectomy 5 5
- Hysterectomy 5 5
- Prostatectomy 5 5

Table (2): Serum Blood Urea Nitrogen Concentration (mg/dl)

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane group (mean±SD)</th>
<th>Isoflurane group (mean±SD)</th>
<th>P Value</th>
<th>St sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre anesthesia</td>
<td>15.7±3.7</td>
<td>14.6±2.5</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Post anesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st day</td>
<td>10.6±2.9</td>
<td>11.4±3.5</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>2nd day</td>
<td>8.9±2.6</td>
<td>9.7±2.5</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>3rd day</td>
<td>11.7±4.1</td>
<td>12.2±4.3</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table (3): Comparison of mean value ± SD serum BUN between pre and post anesthesia in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Pre anesthesia (control)</th>
<th>Post anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st day</td>
<td>2nd day</td>
</tr>
<tr>
<td>Sevoflurane group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean ±SD)</td>
<td>15.7±3.7</td>
<td>10.6±2.9</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isoflurane group</td>
<td>14.6±2.5</td>
<td>11.4±3.5</td>
</tr>
<tr>
<td>(mean ±SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table (4): Serum Creatinine Concentration mg/dl.

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane group (mean ±SD)</th>
<th>Isoflurane Group (mean ± SD)</th>
<th>P Value</th>
<th>St Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre anesthesia</td>
<td>0.74±0.18</td>
<td>0.72±0.13</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
<tr>
<td>Post anesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st day</td>
<td>0.68±0.15</td>
<td>0.72±0.22</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
<tr>
<td>2nd day</td>
<td>0.66±0.16</td>
<td>0.68±0.16</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
<tr>
<td>3rd day</td>
<td>0.58±0.18</td>
<td>0.60±0.11</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
</tbody>
</table>

Table (5): Comparison of mean value ± SD of serum creatinine between pre and post anesthesia both groups.

<table>
<thead>
<tr>
<th></th>
<th>Pre anesthesia (Control)</th>
<th>Post anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st day</td>
<td>2nd day</td>
</tr>
<tr>
<td>Sevoflurane group</td>
<td>0.74±0.18</td>
<td>0.60±0.15</td>
</tr>
<tr>
<td>(mean ±SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Isoflurane group</td>
<td>0.72±0.13</td>
<td>0.71±0.2</td>
</tr>
<tr>
<td>(mean ±SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

915
Table (6) Serum ALT concentration.

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane group (mean ± SD)</th>
<th>Isoflurane group (mean ± SD)</th>
<th>P Value</th>
<th>St Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre anesthesia</td>
<td>18 ±4.8</td>
<td>20 ±7.2</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
<tr>
<td>Post anesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st day</td>
<td>20 ±2.7</td>
<td>21 ±4.3</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
<tr>
<td>2nd day</td>
<td>22 ±10.2</td>
<td>23 ±6.2</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
<tr>
<td>3rd day</td>
<td>20 ±4.8</td>
<td>22 ±5.2</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
</tbody>
</table>

Table (7): Serum AST concentration

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane group (mean ± SD)</th>
<th>Isoflurane group (mean ± SD)</th>
<th>P Value</th>
<th>St Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre anesthesia</td>
<td>20 ±2.2</td>
<td>21 ±8.2</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
<tr>
<td>Post anesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st day</td>
<td>26 ±7.2</td>
<td>28 ±6.4</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
<tr>
<td>2nd day</td>
<td>28 ±91</td>
<td>29 ±6.5</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
<tr>
<td>3rd day</td>
<td>20 ±1.2</td>
<td>21 ±4.6</td>
<td>&gt;0.05</td>
<td>N.S</td>
</tr>
</tbody>
</table>

Fig (1): Urine protein excretion
Discussion

The favorable anesthetic properties of Sevoflurane are well documented and although no case of an adverse renal outcome attributable only to sevoflurane has been reported, its potentiality to cause renal toxicity is still argued (Egar et al., 1997 and Higuchi et al., 1998). To evaluate the renal and hepatic effects of low-flow anesthesia with sevoflurane, we performed low flow sevoflurane in patients having surgery and compared post-anesthesia renal and hepatic functions against that of patients having surgery who received low-flow isoflurane anesthesia. All patients received the same antibiotic at the same dose for three days after surgery, as post-operative antibiotic tends to affect renal function (Gibey et al., 1984). The delivered anesthesia dose, calculated as MAC/ h exposure, and the anesthesia time also did not differ among the two groups. Post anesthesia laboratory tests were performed on day 1, 2 and 3, we chose this time frame because in rat studies, the renal impairment caused by compound A became evident on day 1 after anesthesia, followed by recovery on the fourth day (Gonsowski et al., 1994). However, in study of humans by Higuchi et al., (1995), a small elevation in urinary enzyme NAG after sevoflurane anesthesia was observed on day 2 while Shimada et al., (1990), observed that elevation of urinary enzymes was not seen immediately after renal injury but rather after a delay of 12 to 48 h.

In this study, nitrous oxide was avoided, and opioid concentrations were minimized to increase sevoflurane requirement as compound A concentration are directly proportional to sevoflurane concentration (Morio et al 1992). Barium hydroxide lime was used because compound A formation is greater than with soda lime (Frink et al 1992) Finally, fresh carbon dioxide absorbent was used for every case, because fresh Baralyme produces higher compound A concentration.

We also compared sevoflurane with isoflurane anesthesia because isoflurane is a volatile anesthetic agent that had good safety record for many years.
To measure renal function in surgical patient, the change from preoperative levels in serum creatinine and BUN level is the most practical predictor of post operative renal dysfunction. Charison et al (1989) found that patients who had post operative increases in serum creatinine that sustained for \( \geq 48 \) hours, more than one third of them still had evidence of renal impairment when they left the hospital.

In the present study in which serum creatinine and BUN were used to evaluate renal function in surgical patients treated with sevoflurane compared with isoflurane, there was no significant differences between both groups. These results are similar to previous study of low flow closed circuit sevoflurane, in which serum creatinine and BUN concentrations were unchanged (Bito and Ikeda 1994).

Compound A nephrotoxicity in rats also results in glucosuria and proteinuria, probably resulting from loss of proximal tubular reabsorptive function due to necrosis localized to tubular cell. Gluco-

In this study there was no significant difference in post operative urinary protein excretion between both groups. This agree with the results of Kharasch et al., 1997 who found that there was no significant effect of compound A formation during low-flow sevoflurane on proximal and distal tubular cell integrity.

In this study, the hepatic effects of low flow sevoflurane and isoflurane anesthesia were not significantly differed in both groups. Similar results were reported by Bito and Ikeda 1996 and by Obata et al., 1999.

Human compound A exposure may be compared with those required to elicit nephrotoxicity in rats. The threshold for tubular necrosis was 150-300 ppm-h (part per million -hour) in rats weighing 120-180gm. (Randel et al: 1995).
Compound A concentration which result from exposure to sevoflurane are significantly lower than those used in rats and the maximal inspired compound A concentration in surgical patients at 1L/min fresh gas flow rates range from 8 to 24 ppm-h when soda lime is the CO₂ absorbent and from 20 to 32 ppm-h when baralyme is used (Bito and Ikeda 1994).

Conclusion: there were no significant differences, using conventional and sensitive biomarkers of renal tubular function, between the renal effects of Sevoflurane and Isoflurane in surgical patients undergoing low-flow anesthesia for operation (2-4 h). Also there was no significant differences between the hepatic function in both groups. So low-flow Sevoflurane anesthesia, during which compound A formation occurs, appears to be as safe as low-flow Isoflurane anesthesia.

References


noglycosides and cephalosporins.


