Sevoflurane anaesthesia causes a transient decrease in aquaporin-2 and impairment of urine concentration

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Sevoflurane anaesthesia is occasionally associated with polyuria, but the exact mechanism of this phenomenon has not been clarified. Aquaporin-2 (AQP2) is an arginine vasopressin (AVP)-regulated water channel protein localized to the apical region of renal collecting duct cells and is involved in the regulation of water permeability. To elucidate the effect of sevoflurane anaesthesia on urine concentration and AQP2, we have compared serum and urinary concentrations of AVP, AQP2 and osmolar changes during sevoflurane and propofol anaesthesia.

General anaesthesia was induced with sevoflurane or propofol in 30 patients for a variety of major surgical procedures. Blood and urine samples were obtained from patients at baseline, and 90 and 180 min after induction of anaesthesia. AVP and AQP2 concentrations were measured by radioimmunoassay. In both groups, plasma and urinary concentrations of AVP increased similarly during anaesthesia although plasma osmolality remained unchanged. Although urinary AQP2 excretion in the propofol group increased together with changes in plasma and urinary AVP, urinary AQP2 was significantly lower at 90 min in the sevoflurane group. Urine osmolality in the sevoflurane group also showed a transient but significant decrease in parallel with suppression of AQP2. Our data suggest that sevoflurane anaesthesia transiently produced an impaired AQP2 response to an increase in intrinsic AVP.

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Polyuria is occasionally observed after general anaesthesia with sevoflurane. However, because of the usual abrupt onset and spontaneous remission of polyuria, detailed investigation of this phenomenon has been limited. We reported previously a patient who developed polyuria immediately after surgery under sevoflurane anaesthesia,1 and postulated that many factors, including hormonal and physiological conditions before and during anaesthesia, are involved in the manifestation of the polyuric state. The surgical procedure itself may also specifically induce a marked increase in plasma concentrations of arginine vasopressin (AVP),2 3 independent of changes in plasma osmolality. The surgery-associated increase in AVP is thought to be related to surgical stress3–8 and/or anaesthetic agent.9–11

Aquaporin-2 (AQP2) is an AVP-regulated water channel protein, first discovered in the collecting tubules of the rat kidney in 1993.12 AQP2 was subsequently cloned from the human genome.13 AQP2 is localized in the apical region of collecting duct cells and regulates water permeability in renal collecting ducts.14 15 AQP2 protein is a normal constituent in the urine of normal subjects, and urinary excretion increases after a period of dehydration, decreases after hydration and increases in response to exogenous desmopressin (1-desamino-8-D-arginine vasopressin).16–18 Rai and colleagues19 determined the characteristics of urinary AQP2 and refined the radioimmunoassay (RIA) for this protein, using relatively high concentrations of detergents and bovine serum albumin in the RIA buffer. Using this RIA method, we have shown recently that high concentrations of AVP during surgery under general anaesthesia augments urinary AQP2 excretion.20 Furthermore, our data suggested that anaesthesia probably interfered with this action of AQP2, resulting in a decrease in urine concentration.20

In this study, we have investigated the specific effects of sevoflurane anaesthesia on body fluid balance via AVP-dependent AQP2 in 30 patients undergoing surgery under
general anaesthesia using either sevoflurane or propofol. We measured plasma and urinary AVP and urinary AQP2 concentrations, and the concomitant changes in urinary osmolality.

Patients and methods

The study was approved by the Human Ethics Review Committee of Okayama University Medical School and informed consent was obtained from each patient. We studied 30 patients undergoing various operations under general anaesthesia at our hospital. Patients who required extracorporeal circulation or interruption of blood flow through the aorta, vena cava and renal vessels during surgery were excluded. All patients were premedicated with hydroxyzine 25–50 mg i.m., approximately 30 min before operation. Before anaesthesia, an i.v. line was established in the upper extremity. A urinary catheter and a radial artery catheter were also inserted. Patients were allocated randomly to receive sevoflurane (n=16) or propofol (n=14) for induction of anaesthesia. All patients underwent mechanical ventilation during surgery and were monitored closely. The surgical procedure commenced approximately 20–30 min after induction of anaesthesia. Blood and urine samples were obtained before induction and at 90 and 180 min after initiation of anaesthesia. Blood samples were centrifuged immediately and cells were separated from plasma or serum and stored at –30°C until assay. Urine samples were also stored at –30°C until assay.

Osmolality was measured by freezing point depression. Plasma and urinary AVP concentrations were measured by RIA, and urinary AVP concentrations were corrected for creatinine to the excretion rate of AVP. The RIA for urinary AQP2 was performed using the method described in our previous study.20 Briefly, a synthetic peptide (human AQP2 appropriate (StatView, version 4.5, Abacus Concepts, Berkeley, CA, USA) with Tyr at the N-terminus), radioiodinated [V257-A271] Na (New England Nuclear, Boston, MA, USA) using the chloramine-T method, was mixed with carrier-free [125I] Na and chloramine-T. The reaction was terminated by addition of ascorbic acid followed by 10% KI in distilled water. The mixture was applied to a Sephadex G10 column by addition of ascorbic acid followed by 10% KI in distilled water. The mixture was applied to a Sephadex G10 column.

### Table 1

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sevoflurane group (n=16)</th>
<th>Propofol group (n=14)</th>
</tr>
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<tbody>
<tr>
<td>Median</td>
<td>49.4 (17–74)</td>
<td>54.3 (21–78)</td>
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</table>

<table>
<thead>
<tr>
<th>Sex (M:F)</th>
<th>Sevoflurane group (n=16)</th>
<th>Propofol group (n=14)</th>
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<tr>
<td>M:F</td>
<td>8:8</td>
<td>9:5</td>
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<table>
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<tr>
<th>Total operation time (min)</th>
<th>Sevoflurane group (n=16)</th>
<th>Propofol group (n=14)</th>
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</thead>
<tbody>
<tr>
<td>Median</td>
<td>257.2 (37.6)</td>
<td>398.1 (69.4)</td>
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<tr>
<th>Total anaesthesia time</th>
<th>Sevoflurane group (n=16)</th>
<th>Propofol group (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>336.9 (39.7)</td>
<td>495.0 (68.1)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
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<tr>
<th>Premedication</th>
<th>Sevoflurane</th>
<th>Propofol</th>
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<tbody>
<tr>
<td>Hydroxyzine</td>
<td>25–50 mg</td>
<td>25–50 mg</td>
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<tr>
<th>Induction</th>
<th>Sevoflurane</th>
<th>Propofol</th>
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<tbody>
<tr>
<td>4.25 (0.21)</td>
<td>3–5%</td>
<td>9.83 (0.17) [8–10] mg kg⁻¹ h⁻¹</td>
</tr>
<tr>
<td>+ GO</td>
<td></td>
<td>+ Oxygen</td>
</tr>
<tr>
<td>+ midazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.31 (0.25)</td>
<td>[2–6] mg</td>
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<table>
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<th>Maintenance</th>
<th>Sevoflurane</th>
<th>Propofol</th>
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<tbody>
<tr>
<td>1% Sevoflurane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ GO</td>
<td></td>
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</table>

<table>
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<th>Drug dose during 180 min</th>
<th>Sevoflurane</th>
<th>Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>178.1 (20.9) [100–350] µg</td>
<td>179.2 (16.8) [100–300] µg</td>
</tr>
<tr>
<td>Atropine</td>
<td>0.16 (0.07) [0–0.5] mg</td>
<td>0.21 (0.10) [0–0.05] mg</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>12.63 (1.38) [2–20] mg</td>
<td>15.3 (0.96) [10–20] mg</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>3.13 (0.91) [0–8] mg</td>
<td>8.33 (2.40) [0–28] mg</td>
</tr>
</tbody>
</table>

### Results

Patient characteristics are summarized in Table 1. There were no differences between the sevoflurane and propofol groups in urinary output, volume of blood loss or volume of fluid replacement during the first 180 min of anaesthesia. Fluid replacement consisted of lactated Ringer’s solution, acetate solution and saline. No blood or plasma was transfused. Mean urine excretion rate and total operation time were similar in both groups, but the total duration of anaesthesia was significantly longer in propofol than in the sevoflurane group. The operative region included the abdomen, thorax, bones and joints, or the head and neck (Table 1) in both groups.

Polyuria or polydipsia was not observed either before or after anaesthesia in any patient. Drugs used during anaesthesia are listed in Table 2. Sixteen patients were anaesthetized with sevoflurane using the following procedure. Anaesthesia
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unchanged at 90 min (relative to baseline) in both groups but significantly increased at 180 min in both groups (Fig. 1b). Plasma and urine AVP concentrations at 180 min after induction of anaesthesia in the sevoflurane and propofol groups were 4.72 (2.0) and 5.29 (2.3) pg ml⁻¹ and 106.3 (44.7) and 113.7 59.2 ng gCr⁻¹, respectively, indicating that both agents were associated with a similar increase in plasma and urinary AVP concentrations.

Baseline urinary AQP2 excretion was 177.1 (29.9) and 160.6 (30.4) fmol mgCr⁻¹ in the sevoflurane and propofol groups, respectively (Fig. 1c). At 90 min after induction of anaesthesia, urinary AQP2 concentration in the sevoflurane group was low (136.5 (20.9) fmol mgCr⁻¹) while that in the propofol group was significantly high (259.9 (48.9) fmol mgCr⁻¹) relative to baseline. The difference in AQP2 between groups was significant. At 180 min after induction of anaesthesia, urinary AQP2 excretion in the sevoflurane group was significantly elevated (247.2 (43.2) fmol mgCr⁻¹) and remained elevated in the propofol group (280.1 (47.7) fmol mgCr⁻¹) relative to baseline.

Plasma osmolality and serum sodium concentrations remained stable throughout the study and there were no significant differences between groups (Fig. 2A, B). Baseline urine osmolality was comparable in the two groups. At 90 min after induction of anaesthesia, urine osmolality decreased in both groups. However, it was significantly lower in the sevoflurane group compared with the propofol group and baseline (Fig. 2C). At 180 min after induction of anaesthesia, urine osmolality tended to be lower in both groups relative to baseline, although there was no difference between groups. A similar trend was observed in urinary sodium excretion, although the changes did not reach statistical significance (Fig. 2D).

Discussion

One of the most important functions of the kidney is regulation of body fluid balance by concentrating or diluting urine. Such regulatory processes depend on the presence of a discrete segmental distribution of transport properties along the renal tubules and collecting ducts. Recently, several proteins responsible for these properties have been cloned. Among these (also known as aquaporins), AQP2 mediates water transport across the apical plasma membrane of principal cells and is the main target for the short-term action of AVP to increase water permeability. Most of the AQP2 molecules are present in cytoplasmic vesicle membranes rather than in the apical membrane of the renal collecting ducts and AQP2 in the apical membrane was considered to be the active molecule for concentrating urine. Approximately 3% of AQP2 present in the kidney is constantly excreted from the apical membrane into urine each day and this fraction does not change even during dehydration. These findings imply that the amount of AQP2 excreted in urine reflects the mechanism for regulating AQP2 protein in the apical membrane.

was induced with 3–5% sevoflurane with nitrous oxide in oxygen using a semi-closed circuit, in addition to midazolam. Anaesthesia was maintained with approximately 1% sevoflurane with nitrous oxide in oxygen. Propofol anaesthesia was used in 14 patients. Anaesthesia was induced with propofol 8–10 mg kg⁻¹ h⁻¹ and oxygen, followed by maintenance with 2–5 mg kg⁻¹ h⁻¹ and nitrous oxide in oxygen. During the study period of 180 min, fentanyl, atropine, vecuronium and ephedrine were also administered. The doses of these drugs were not different between groups, with the exception of ephedrine. A higher dose was used in the propofol group as anaesthesia tended to induce hypotension. None of the 30 cases showed marked changes in mean arterial pressure (decreases exceeding 5%) or cardiac dysfunction over the 180 min.

Plasma and urinary AVP concentrations before anaesthesia in the sevoflurane and propofol groups were 1.57 (0.2) and 1.02 (0.2) pg ml⁻¹ and 28.2 (7.5) and 23.7 (7.0) ng gCr⁻¹, respectively (Fig. 1a, b). Anaesthesia was associated with a change in plasma and urinary AVP concentrations. In both groups, plasma AVP was higher at 90 min, although no further increase was noted at 180 min (Fig. 1a). In contrast, urinary concentrations of AVP were unchanged at 90 min (relative to baseline) in both groups but significantly increased at 180 min in both groups (Fig. 1b). Plasma and urine AVP concentrations at 180 min after induction of anaesthesia in the sevoflurane and propofol groups were 4.72 (2.0) and 5.29 (2.3) pg ml⁻¹ and 106.3 (44.7) and 113.7 59.2 ng gCr⁻¹, respectively, indicating that both agents were associated with a similar increase in plasma and urinary AVP concentrations.

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Sevoflurane anaesthesia suppresses aquaporin-2

Fig 2 Changes in plasma osmolality (A), serum sodium concentrations (B), urine osmolality (C) and urinary sodium excretion (D) before (Pre.) and during anaesthesia. Data are mean (SEM). *P<0.05 vs baseline; ‡P<0.05 between groups.

measurement of urinary excretion of AQP2 protein is now possible, and detectable concentrations and changes in response to AVP can be measured by RIA. Thus measurement of urinary AQP2 excretion is helpful for overall evaluation of body fluid balance.

In addition to changes in osmolality, several other factors stimulate secretion of AVP from the posterior pituitary. These include reduction in circulating blood volume, reduction in mean arterial or left atrial pressure, various peptides, including catecholamines, angiotensin II, atrial natriuretic peptide and prostaglandins, drugs with cholinergic or β-adrenergic properties, opioids and anaesthesia. Furthermore, high plasma AVP concentrations have been demonstrated in patients undergoing anaesthesia for surgery, only after initiation of the surgical procedure. Therefore, the surgical operation under general anaesthesia represents an endocrinologically specific condition characterized by inappropriate oversecretion of AVP. This is thought to be caused by surgical stress and/or anaesthetic agent.

In our study, although concentrations of AVP were not different between the sevoflurane and propofol groups, the increase in urinary AQP2 was significantly blunted in the sevoflurane group compared with the propofol group. Furthermore, differences in urine osmolality reflected the difference in AQP2 excretion, that is urine concentrating capacity was also impaired during sevoflurane anaesthesia in contrast with propofol anaesthesia. The differential response of AQP2 and urine osmolality to sevoflurane was prominent at 90 min after induction of anaesthesia; differences in urinary AQP2 and osmolality between the two anaesthetics were not significant at 180 min. Sevoflurane is a volatile, fluorinated anaesthetic agent which is occasionally associated with polyuria; however, the pathogenesis of polyuria is elusive. It is not clear if sevoflurane causes renal impairment, although it has been used in more than 2 million operations in Japan.

Biotransformation of fluorinated volatile anaesthetics results in the production of fluoride metabolites, which may be associated with hepatic or renal toxicity. Sevoflurane undergoes hepatic biotransformation in humans, producing peak plasma inorganic fluoride concentrations equivalent to those associated with renal impairment after methoxyflurane anaesthesia. Although in the case of methoxyflurane, biotransformation by renal cytochrome P450 is believed to be associated closely with renal damage, most clinical studies have not reported fluoride-associated nephrotoxicity with sevoflurane anaesthesia.

Jellish and colleagues demonstrated recently a small but significant decrease in urine specific gravity, an indirect measure of renal concentrating ability, 24 h after exposure to sevoflurane compared with propofol. In another study, Higuchi and colleagues showed that administration of vasopressin i.v., 16.5 h after cessation of anaesthesia, caused a slight and insignificant reduction in urinary osmolality in sevoflurane-anaesthetized patients whose fluoride concentration was more than 50 µmol litre⁻¹. These findings suggest that sevoflurane may alter the urine concentrating capacity of the renal collecting ducts. In our study, we demonstrated transient suppression of urinary AQP2 and impairment of urine concentration during sevoflurane anaesthesia, but these changes were no longer significant 180 min after induction of anaesthesia. What are the mechanisms of sevoflurane-induced suppression of urinary AQP-2? Several
mechanisms are involved in AQP2 mobilization to the apical membrane of the renal collecting duct cells in response to AVP. These mechanisms play an important role in increased water permeability.\textsuperscript{14, 15} It is possible that these shuttle trafficking mechanisms are transiently interrupted by sevoflurane anaesthesia. Impaired urine concentration observed in our study may contribute to the cause of polyuria occasionally noted after sevoflurane anaesthesia. Namely, when this transient impairment of urine concentration is prolonged or modified by administration of other medications, polyuria may become clinically evident.

To avoid the influence of other drugs on water balance, our study was designed using common medications and routine procedures, and the main variable was the anaesthetic agent. One exception was the use of ephedrine. As shown in Table 2, a higher dose of ephedrine was required during propofol anaesthesia to maintain a constant arterial pressure. Ephedrine has both direct and indirect agonist actions on $\alpha$ and $\beta$ receptors and the indirect action is via release of norepinephrine from presynaptic sites.\textsuperscript{33} The effects of ephedrine on renal haemodynamics and electrolyte handling are controversial. Westman, Hamberger and Jörnberg\textsuperscript{34} studied these effects during surgical procedures similar to ours, and found that urine flow, renal plasma flow, glomerular filtration rate and fractional clearance of sodium were increased significantly in addition to a significant increase in systemic arterial pressure with ephedrine 2–6 $\mu$g kg$^{-1}$ min$^{-1}$. The noticeable finding in their study was the negative effect of ephedrine at the same dose on both osmolar and free water clearances, indicating AVP activity.\textsuperscript{34} In our study, mean doses of ephedrine in the sevoflurane and propofol groups were 0.3 (maximum 0.9) $\mu$g kg$^{-1}$ min$^{-1}$ and 0.9 (maximum 3.8) $\mu$g kg$^{-1}$ min$^{-1}$, respectively, which were much smaller than those in the study of Westman, Hamberger and Jörnberg.\textsuperscript{34} Although we cannot exclude the possibility that the effect of ephedrine was on urinary sodium excretion, the change in osmolality of urine may not have been affected by the small dose of ephedrine used in our study. As for the effect of ephedrine on AVP secretion, Ramin and colleagues\textsuperscript{35} reported that the use of ephedrine 10 mg during regional anaesthesia at delivery increased plasma AVP concentration compared with general anaesthesia. But in our study, plasma and urinary AVP concentrations were not significantly different between the two anaesthetic procedures. The doses of other drugs and the in–out balance of body fluid over 180 min did not differ between groups. Thus our data most likely reflected the differences between sevoflurane and propofol. However, the effect of other procedures, drugs or fluid imbalance cannot be ruled out completely.

In summary, we have demonstrated that sevoflurane suppressed urinary excretion of AQP2 and reduced urinary concentration during surgery compared with propofol anaesthesia, although both were associated with an increase in plasma AVP. These results indicate that sevoflurane anaesthesia transiently blunts the urine concentrating capacity of the kidney by reducing AQP2. Our findings suggest that sevoflurane-associated polyuria is caused by impairment of the AQP2 response to an increase in AVP during surgery.

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