Sevoflurane is a volatile anaesthetic with a relatively low blood:gas partition coefficient of 0.63, compared with 1.90 and 2.40 for enflurane and halothane, respectively [1]. It has a pleasant, non-pungent odour, which permits smooth and rapid inhalation induction. It should be suitable, therefore, for neurosurgical patients, in whom rapid induction and recovery are often desired. Sevoflurane is an ether anaesthetic and there is some concern that it may induce seizure activity, in common with enflurane [2], particularly in the presence of hypocapnia. However, it was not found to induce seizure activity in dogs at 1.5, 2.0 and 2.5 MAC during normocapnia or hypocapnia, even in the presence of intense auditory stimuli [3]. Scheller and colleagues found that the effects of sevoflurane on cerebral blood flow (CBF), cerebral metabolic rate for oxygen (CMRO₂), intracranial pressure (ICP) and the EEG were similar to those of isoflurane in normocapnic rabbits [4]. However, its effects on ICP and cerebral perfusion pressure (CPP) during hypocapnia have not been studied. We have therefore compared the effects of sevoflurane, enflurane and halothane on ICP, CPP and the cardiovascular system in hypocapnic dogs.

MATERIAL AND METHODS

This study was approved by The Animal Care and Use Committee at the Hamamatsu University School of Medicine. We studied 24 unmedicated mongrel dogs (weights 5-12 kg). Anaesthesia was induced with sodium pentobarbitone 30 mg kg⁻¹ and pancuronium 0.2 mg kg⁻¹. The trachea was intubated and the lungs ventilated with 60 % nitrous oxide in oxygen; P_{CO₂} was maintained in the normal range (4.9-5.3 kPa). The animals were placed in the supine position and the right femoral artery was cannulated for measurement of arterial pressure and blood sampling. The right external jugular vein was cannulated for measurement of central venous pressure (CVP) and administration of fluids and drugs.

Surgical preparation was carried out in all cases after local infiltration of 0.25 % bupivacaine.

A Burr hole 10 mm in diameter was drilled in the right parietal area and a small catheter was inserted into the subdural space for measurement of ICP. A drop of cyanoacrylate cement was used to seal the dura.

Measured variables included mean arterial pressure (MAP), heart rate (HR), CVP, ICP, end-tidal concentrations of volatile anaesthetic (measured at the distal end of endotracheal tube), carbon dioxide and oxygen, and arterial blood-gas tensions. CPP was calculated as the difference between MAP and ICP (at the level of the head).

End-tidal concentrations of carbon dioxide and volatile anaesthetic were recorded using a mass spectrometer (Perkin–Elmer MGA 1100; Perkin-Elmer, Pomano, CA). Rectal temperature was maintained at 36.5-37.5 °C with a heating blanket. Ringer lactate solution was infused i.v. at 5 ml kg⁻¹ h⁻¹.

The animals were left undisturbed for 30 min before baseline (control) measurements were made, with P_{CO₂} maintained at normocapnia. Hyperventilation was induced by increasing the rate of ventilation and P_{CO₂} was maintained at 3.2-3.7 kPa for at least 15 min. The animals were then allocated randomly to receive halothane (n = 8), enflurane (n
TABLE I. Mean (SEM) intracranial pressure (ICP), cerebral perfusion pressure (CPP), mean arterial pressure (MAP) and volatile anaesthetic concentrations (S = sevoflurane; E = enflurane; H = halothane). Normocapnia = arterial carbon dioxide tension 4.9–5.3 kPa; hypocapnia = arterial carbon dioxide tension 3.2–3.7 kPa. Significantly different from control values: *P < 0.05; **P < 0.01. Significantly different from sevoflurane values: †P < 0.05; ††P < 0.01.

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<th>Normocapnia, control</th>
<th>Hypocapnia, pre-exposure</th>
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<td>S  E  H</td>
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<td>ICP (mm Hg)</td>
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<td></td>
<td>5.1 (0.7) 6.6 (0.7) 7.6 (0.7)</td>
<td>3.8 (0.7) 5.0 (0.3) 5.6 (0.4)</td>
<td>5.0 (0.9) 10.3 (1.0)** †† 12.0 (1.4)** ††</td>
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<td>CPP (mm Hg)</td>
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<td></td>
<td>120 (5) 125 (8) 118 (5)</td>
<td>119 (7) 128 (6) 122 (6)</td>
<td>105 (7)* 62 (5)** 92 (6)**</td>
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<td>MAP (mm Hg)</td>
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<td>125 (5) 131 (8) 125 (5)</td>
<td>123 (6) 133 (6) 128 (5)</td>
<td>110 (6)* 93 (6)** 104 (5)**</td>
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<th>Hypocapnia, 1.0 MAC</th>
<th>Hypocapnia, 1.5 MAC</th>
<th>Hypocapnia, post-exposure</th>
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<td>ICP (mm Hg)</td>
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<td>5.6 (1.2) 10.6 (0.6)** †† 12.0 (1.2)** ††</td>
<td>6.4 (1.4) 10.0 (0.8)** 11.8 (1.1)** †</td>
<td>5.3 (0.9) 7.8 (0.8) 8.8 (0.8)†</td>
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<td>CPP (mm Hg)</td>
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<td></td>
<td>88 (6)** 57 (5)** †† 73 (5)**</td>
<td>68 (5)** 38 (4)** †† 59 (5)**</td>
<td>112 (11) 111 (8) 102 (5)*</td>
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<td>MAP (mm Hg)</td>
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<td></td>
<td>95 (5)** 68 (5)** †† 85 (5)**</td>
<td>75 (4)** 48 (5)** †† 68 (4)**</td>
<td>117 (10) 119 (8) 111 (5)*</td>
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**P < 0.01 compared with control. †P < 0.05, ††P < 0.01 compared with sevoflurane. Normo. = normocapnia.

Fig. 1. Mean (SEM) changes in intracranial pressure (ICP) with sevoflurane (●), enflurane (○) or halothane (△).

= 8) or sevoflurane (n = 8) (one volatile anaesthetic per animal), administered at 0.5 MAC end-tidal concentration. Measurements of variables were repeated 15 min later. The end-tidal concentration of the anaesthetic was increased to 1.0 MAC and 1.5 MAC for at least 15 min and all measurements repeated. The volatile anaesthetic was then discontinued. Twenty minutes later, all measurements were repeated using only a background anaesthetic of nitrous oxide.

MAC values were: sevoflurane 2.36%, enflurane 2.2%, halothane 0.89% [5].

Statistical analysis

All data were expressed as mean (SEM). pH, PaCO₂, PaO₂, ICP, CPP, MAP, HR and CVP were compared within groups at the six anaesthetic states using a repeated measures analysis of variance followed by Dunnett’s test [6] (comparison with control) where appropriate. pH, PaCO₂, PaO₂, ICP, CPP, MAP, HR and CVP were compared between the three anaesthetic agents at comparable MAC values by analysis of variance and, where differences were detected, pair-wise comparisons (sevoflurane with enflurane, sevoflurane with halothane) were performed using Student’s t test for unpaired data with the Bonferroni correction for multiple comparisons. Changes were considered significant at P < 0.05.

RESULTS

ICP, CPP and MAP data are shown in table I. There were no intergroup differences in mean PaCO₂, PaO₂ and pH values at which ICP, CPP, MAP, HR and
CVP were compared: hyperventilation had no significant effect on $P_{aco_2}$, which remained in the range 24.7 (2.4)–28.8 (2.0) kPa, but caused pH to increase to 7.43 (0.01)–7.49 (0.03) and $P_{aco_2}$ to decrease to 3.2 (0.4)–3.7 (0.1) kPa.

There were no intergroup differences in ICP before administration of volatile agents. ICP increased significantly with 0.5, 1.0 and 1.5 MAC enflurane and halothane, but not with sevoflurane in any anaesthetic concentration (fig. 1). After discontinuation of the volatile anaesthetic, ICP remained significantly greater in the halothane than in the sevoflurane group.

Hyperventilation caused no change in CPP or MAP. Addition of the volatile anaesthetics caused a significant decrease in CPP (fig. 2) and MAP (fig. 3). There was no difference in the rate of decrease in arterial pressure with all three agents. In the sevoflurane and enflurane groups, CPP and MAP returned to the initial baseline values after discontinuation of the volatile anaesthetic. In the halothane group, CPP and MAP did not return to control values.

There were no intergroup differences in HR and CVP at any anaesthetic level. Hyperventilation had no significant effect on HR, which ranged from 152 to 169 beat min$^{-1}$, or CVP (1.4–2.1 mm Hg). HR decreased significantly with 1.0 and 1.5 MAC of sevoflurane and halothane, and 0.5, 1.0 and 1.5 MAC of enflurane.

**DISCUSSION**

During halothane anaesthesia, the vasoconstrictor effect of hypocapnia exceeds the vasodilator effects of the volatile anaesthetic [7]. When hypocapnia ($P_{aco_2}$ less than 4 kPa at normothermia) is produced in patients with intracranial lesions, the effects of subsequent administration of 0.5–1.0% halothane on ICP are consistently blocked. However, simultaneous administration of hyperventilation and halothane does not always prevent a large increase in ICP [7]. Although enflurane is a less potent cerebral vasodilator than halothane, it has been shown to increase CBF [2] and ICP [8, 9] in both animals and humans. Enflurane may be used for patients with intracranial pathology if hypocapnia is induced before its administration [10]. Isoflurane is the least potent cerebral vasodilator compared with enflurane or halothane and thus has least effect on CBF [11, 12] and ICP [13, 14]. Although isoflurane causes an increase in ICP in patients with intracranial space-occupying lesions, in contrast with halothane, it is not necessary to establish hypocapnia before administration of the drug [13]. Isoflurane and sevoflurane are comparable in their capacities to increase ICP in
normocapnic rabbits [4]. The response of canine cerebral circulation to hyperventilation during anaesthesia with sevoflurane has not been examined.

In this study, we have shown that enflurane and halothane caused significant increases in ICP at 0.5, 1.0 and 1.5 MAC despite prior establishment of hypocapnia, while sevoflurane had no effect in any concentration. These data for halothane and enflurane conflict with those reported previously [7, 10]. There are several explanations for these discrepancies.

First, the present study was conducted in dogs with normal intracranial compliance, but one previous study [7] was performed on humans with supratentorial mass lesions. Second, in that study [7], measurement of ICP was made, not in the intracranial space, but in the lumbar subarachnoid space. Third, as the authors did not measure the end-tidal concentration of halothane, it is likely that their patients received halothane in concentrations less than 1.2 MAC.

Previous studies have reported an increase in ICP in rabbits [4] and dogs [3] after administration of sevoflurane. In common with isoflurane, sevoflurane has been shown to have minimal effect on CBF [3, 4]. Its effects of ICP in our study were essentially the same as those reported for isoflurane [13]. Isoflurane may cause a dose-related increase in CBF [15] accompanied by an increase in ICP [16], both of which may be attenuated by hyperventilation [17].

ICP increases in response to changes in either CBF or cerebrospinal fluid (CSF) volume. The effects of sevoflurane on CBF have been reported, but effects on cerebral blood volume (CBV) and CSF dynamics remain unclear. During isoflurane anaesthesia, hyperventilation decreases CBV, resulting in decreased ICP. Although CBV gradually increases with exposure to isoflurane, this change is opposed by a decrease in CSF volume; thus there is no net increase in ICP [18]. In contrast with enflurane [19], isoflurane has no significant effect on rate of production of CSF [20] and decreases resistance to the reabsorption of CSF in the dog. Hyperventilation apparently has no significant effect on this particular component of ICP [21].

Our study has shown that all three volatile agents caused significant decreases in MAP and CPP with increasing anaesthetic concentrations. There was no difference in the rate of change in arterial pressure with the three agents. The increase in ICP with enflurane and halothane commenced before the arterial pressure decrease and thus we believe the increase in ICP with these two agents was caused by a direct vasodilatation of cerebral vessels. With 1.0 and 1.5 MAC enflurane anaesthesia, MAP decreased markedly compared with sevoflurane and CPP consequently decreased to less than 50 mm Hg (figs 2, 3), the lower end of the autoregulatory range. Thus it is possible that small concentrations of inhalation anaesthetics may be used safely during anaesthesia for intracranial operation on patients with brain tumours, provided that arterial pressure is monitored carefully. The effects of these agents on MAP may facilitate control of arterial pressure and the induction of hypotension during neurosurgery.


20. Artru AA. Isoflurane does not increase the rate of CSF production in the dog. *Anesthesiology* 1984; 60: 193-197.


