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Desflurane results in higher cerebral blood flow than sevoflurane or isoflurane at hypocapnia in pigs

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Background: In clinical neuroanaesthesia, the increase in cerebral blood flow (CBF) and intracranial pressure caused by the cerebral vasodilative effects of an inhalational anaesthetic agent is counteracted by the cerebral vasoconstriction induced by hypocapnia. Desflurane and sevoflurane may have advantages over the more traditionally used isoflurane in neuroanaesthesia but their dose-dependent vasodilative effects at hypocapnia have not been compared in the same model using truly equipotent minimal alveolar concentrations (MACs).

Method: Desflurane, sevoflurane and isoflurane were administered in a randomized order to six pigs at 0.5 and 1.0 MAC. The intra-arterial xenon clearance technique was used to calculate CBF. Blood pressure was invasively monitored. Cerebral and systemic physiological variables were recorded first at normocapnia (PaCO₂ 5.6 kPa) and then at hypocapnia (PaCO₂ 3.5 kPa). Electroencephalographic (EEG) activity was continuously recorded.

Results: None of the three agents abolished cerebrovascular reactivity to hyperventilation, and at 0.5 MAC all had similar

effects on CBF at hypocapnia. Desflurane at 1.0 MAC was associated with 16% higher CBF ($P=0.027$) at hypocapnia than isoflurane, and with 24% higher CBF ($P=0.020$) than sevoflurane. There was no seizure activity in the EEG.

Conclusion: More cerebral vasodilation at hypocapnia with high doses of desflurane than with sevoflurane or isoflurane indicates that desflurane might be less suitable for neuroanaesthesia than sevoflurane and isoflurane.

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Key words: Anaesthesia; cerebral blood flow; cerebrovascular reactivity; desflurane; inhalational; isoflurane; sevoflurane; swine.

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PRESERVED cerebrovascular reactivity to hypocapnia is important in neuroanaesthetic practice, since the cerebral vasodilation induced by halogenated volatile anaesthetic agents (1,2) may raise intracranial pressure (ICP) in patients with reduced intracranial compliance. Such increases in ICP are normally counteracted by cerebral vasoconstriction resulting from hyperventilation. Isoflurane remains the inhalational agent of choice in clinical neuroanaesthesia since its cerebral haemodynamic effects are well known, whereas corresponding use of desflurane and sevoflurane is still under debate (3,4). Equipotent minimum alveolar concentration (MAC) values are required to reliably compare volatile anaesthetics with respect to their dose-dependent adverse effects (2–4).

The aim of the present investigation was comparison of the effects of desflurane, sevoflurane and isoflurane on CBF at hypocapnia at equipotent MAC levels in an established experimental model with intact intracranial compliance.

Materials and methods

The Ethics Committee of Animal Studies at Lund University approved the study protocol, and the experiments were carried out at the Department of Experimental Research, Malmö University Hospital, Lund University, Sweden.

Procedures

Six juvenile pigs of Swedish domestic breed (mean weight \pm SEM, 20.3 \pm 0.8 kg) were used. The pigs were fasted over night but had free access to water.

The animals were anaesthetized with 200 mg of propofol and 8 mg of vecuronium intravenously (i.v.), endotracheally intubated and ventilated with an oxygen-nitrogen mixture containing 40% of oxygen in a rebreathing anaesthesia circuit fitted with a soda lime absorber and a bag-in-bottle ventilator. Desflurane was administered with an Ohmeda Tec 6 vaporizer (Ohmeda, Helsinki, Finland), whereas sevoflurane

Table 1

The order in which each of the six animals was exposed to the study drugs.

Experimental animal number	Study drug administered during		
	first exposure	second exposure	third exposure
1	sevoflurane	isoflurane	desflurane
2	sevoflurane	desflurane	isoflurane
3	desflurane	isoflurane	sevoflurane
4	desflurane	sevoflurane	isoflurane
5	isoflurane	sevoflurane	desflurane
6	isoflurane	desflurane	sevoflurane

and isoflurane were administered with Penlon vaporizers (Penlon, UK). Inspiratory and expiratory contents of oxygen, carbon dioxide and inhalational agent were monitored with an Ohmeda 5250 RGM side-stream agent monitor (Ohmeda, Helsinki, Finland). Vaporizers and agent monitor were calibrated by the Department of Medical Technology, Malmö University Hospital, before the experiments. An external Warmtouch™ heating device (Mallinckrodt, Northampton, UK) was used to keep body temperature within a physiological range ($38.1 \pm 0.1^\circ\text{C}$) throughout experiments. Muscle paralysis was maintained by i.v. infusion of $1.0 \text{ mg kg}^{-1} \cdot \text{h}^{-1}$ of vecuronium. Each animal was given all three drugs in a predetermined even crosswise order (Table 1) after exposure to 1.0–1.3 MAC of the first agent also used for anaesthesia during surgical preparation.

The MAC values used here – $13.8 \pm 0.4\%$ for desflurane, $4.4 \pm 0.1\%$ for sevoflurane and $2.7 \pm 0.1\%$ for isoflurane – had been determined in a previous investigation (2).

Surgical preparation has recently been extensively described (2) and is reported briefly here. The internal carotid artery was cannulated for intra-arterial injection of tracer substance (^{133}Xe) for measurements of CBF, which was calculated (Novo Cerebrograph 10a, B Simonsen Medical AS, Denmark) from the cerebral washout pattern of the tracer as recorded by an external NaI scintillation detector. Unless some artefact tainted the washout curve, only one injection of tracer was made at each measure point. The reliability of this model for repeated measurements of CBF with the xenon washout technique has previously been verified (5, 6). Bipolar electroencephalographic (EEG) signals were recorded by two pairs of needle electrodes, inserted subcutaneously over frontal and occipital regions of the cerebral hemispheres, with a ground electrode inserted subcutaneously in the neck. The signals were amplified (amplification factor: 10^4), filtered (high pass: limit 0.5 Hz; low pass: limit 30 Hz), continuously recorded and digitally stored. Systemic haemodynamics were invasively monitored, and temperature was measured.

Infusion of 500 ml of a 6% solution of hydroxyethyl starch (Haes-steril, Meda, Sweden) was given i.v. during preparation to compensate for surgical blood loss and optimize haemodynamic stability, and a further 250 ml was infused during the rest of the experiment. In addition, a balanced 2.5% glucose solution was infused at a rate of $4\text{--}5 \text{ ml kg}^{-1} \cdot \text{h}^{-1}$ during the entire experiment.

All animals were given all three agents in sequence (Table 1, Fig. 1) and received first 0.5 and then 1.0 MAC of the present agent. Each series of measurements was preceded by a 60-min equilibration period with 0.5 MAC of the intended agent and normoventilation with 6 l min^{-1} of fresh gas flowing through the anaesthesia circuit. Measurements were made when equilibration had been long enough to reduce the difference between inspired and expired concentrations of each study drug at the desired MAC level to no more than 0.3% for desflurane and to no more than 0.1% for sevoflurane or isoflurane. Measurements were made first at normocapnia and then at hypocapnia induced by increasing ventilation by 50% for at least 15 min. Ventilation was titrated according to blood gas analyses to achieve the desired level of PaCO_2 —5.6 kPa for normocapnia and 3.5 kPa for hypocapnia. Experiments lasted between 9 and 11 h.

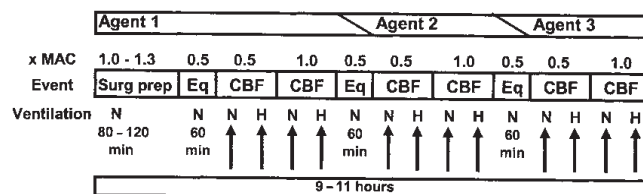


Fig. 1. The experimental procedure. After intravenous induction with propofol, surgical preparation ('Surg prep') was performed and after a 60-min equilibration period ('Eq'), measurements were started with the first inhalational anaesthetic agent ('Agent 1'). Between each of the three inhalational agents ('Agent 1', 'Agent 2', 'Agent 3') there was an equilibration period (60 min). The inhalational agents were given one at a time with the administered dose being a fraction (0.5, 1.0 or 1.0–1.3) of the minimal alveolar concentration (MAC) value for that agent. Cerebral blood flow (CBF) and systemic haemodynamic pressures were recorded (measuring points indicated by arrows) at both normocapnia (N) and hypocapnia (H).

Invasive intracranial measurements were avoided in the present study to avoid possible interference with normal intracranial compliance.

At each point of measurement, CBF, mean arterial blood pressure (MAP) and core temperature were measured. Corresponding EEG recordings were analyzed for potential patterns of seizure activity or burst suppression.

Statistical methods

>Statistical power analysis, using paired comparisons, showed that six animals would be required to detect a 10–15% difference in CBF between the study drugs at hypocapnia with a power of 80% and a probability of 95%.

Results are given as mean \pm 1 standard error of the mean (SEM). A repeated measure ANOVA with Bonferroni-correction was used for comparisons between agents. Paired *t*-test with Bonferroni-correction was used for comparisons of hypocapnic data to normocapnic data. The level of statistical significance was $P < 0.05$. Statistical analyses were made with the SPSS for Windows software, release 11.5.1 (SPSS Inc, Chicago, IL).

Results

For all three drugs CBF (Fig. 2) was significantly lower at hypocapnia compared with normocapnia at both 0.5 and 1.0 MAC. MAP (Fig. 3) was not significantly different between the two PaCO₂ levels for any of the three drugs.

The agents did not differ significantly in their effect on CBF (Fig. 2) at hypocapnia at 0.5 MAC. However, at hypocapnia and 1.0 MAC, CBF with desflurane was 16% higher than with isoflurane ($P = 0.027$) and 24% higher than with sevoflurane ($P = 0.020$). Sevoflurane and isoflurane did not differ significantly in effects on CBF.

With desflurane, MAP (Fig. 3) was 22% lower at 0.5 MAC ($P = 0.020$) and 17% lower at 1.0 MAC ($P = 0.030$) than with sevoflurane, whereas no other significant differences in effects on MAP were found between the study drugs.

There was no seizure activity in the EEG for any study drug at any ventilation modality. At 1.0 MAC, but not at 0.5 MAC, there were burst suppression patterns for all study drugs in all animals.

Discussion

Experimental design

Isoflurane is the ideal agent for reference when studying newer inhalational agents since it is often the inhalational agent of choice in clinical neuroanaesthesia (3, 4). Desflurane and sevoflurane have been compared to isoflurane in various neuroanaesthesiological aspects (1, 2, 7–9), but discussion continues regarding desirable and undesirable effects (3, 4). Negative side-effects of inhalational agents such as cerebral vasodilation and attenuation of vasoreactivity to hypocapnia are dose-dependant (1, 9, 10), and reliable comparison between agents of these effects

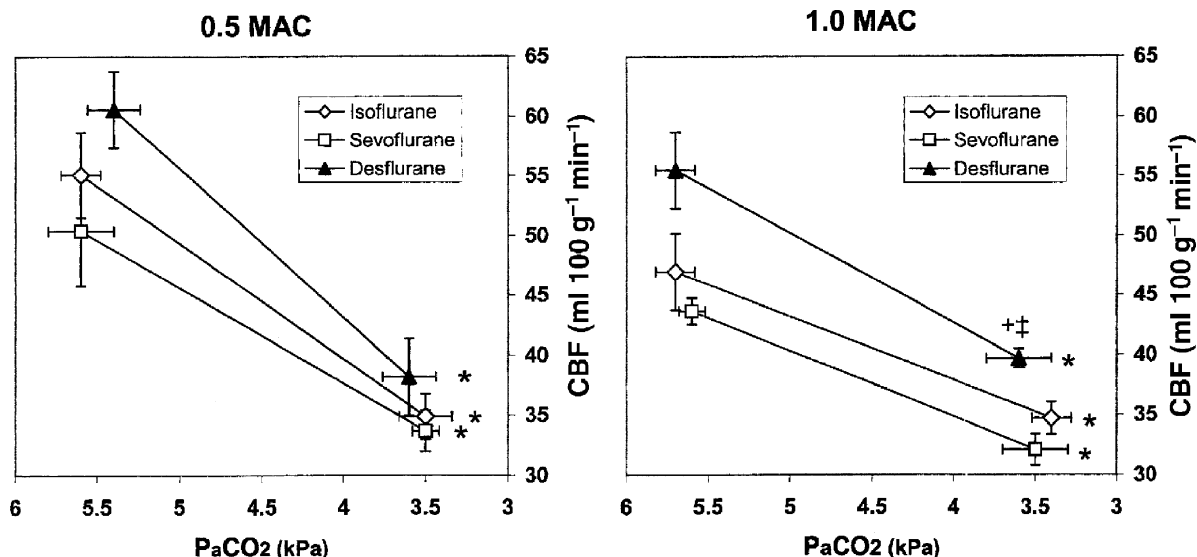


Fig. 2. Cerebral blood flow (CBF) at normocapnia and hypocapnia (mean \pm SEM, $n = 6$) at 0.5 and 1.0 minimal alveolar concentrations (MACs) for the three studied inhalational agents desflurane, sevoflurane and isoflurane. Significant differences ($P < 0.05$) between normocapnia and hypocapnia are indicated by *, between desflurane and isoflurane by +, and between desflurane and sevoflurane by \pm .

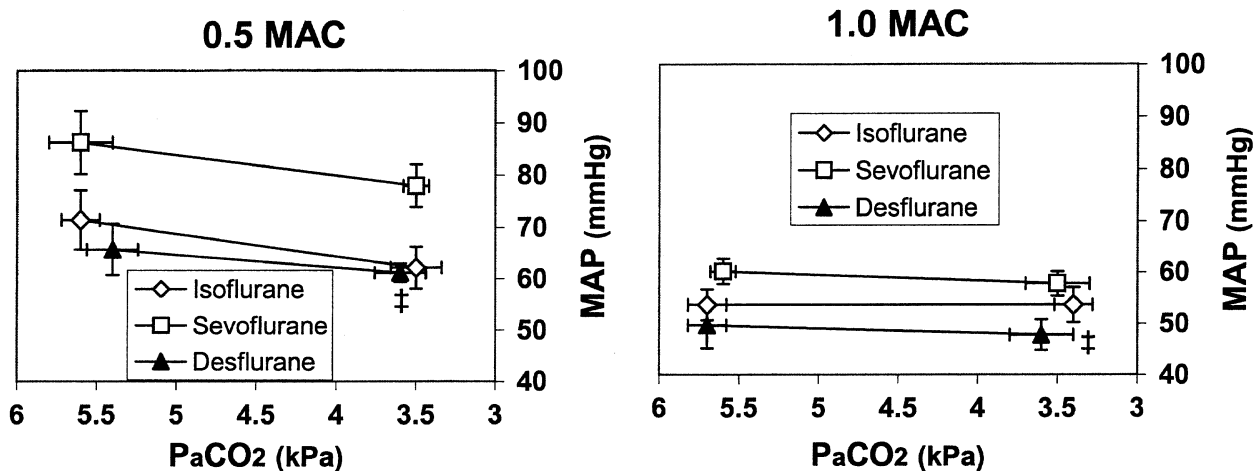


Fig. 3. Mean arterial pressure (MAP) at normocapnia and hypocapnia (mean \pm SEM, $n = 6$) at 0.5 and 1.0 minimal alveolar concentrations (MAC) for desflurane, sevoflurane and isoflurane. No statistically significant differences exist between normocapnia and hypocapnia in terms of effects on MAP. Significant differences ($P < 0.05$) between desflurane and sevoflurane are indicated by ‡.

with the level of anaesthesia defined by MAC consequently requires equipotent MAC values. Since MAC is highly method- and species-dependent, with values varying considerably (2, 11–13), comparable MAC values for the three drugs compared here had been obtained in a recent study (2).

Invasive intracranial measurements requiring cranial burr-holes and dural incisions were avoided due to the risk of compromising the aim of the study – comparison of the cerebrovascular effects of the three anaesthetic agents at hypocapnia with no other influence on intracranial compliance than from the study drugs themselves. Invasive intraparenchymal monitoring of intracranial pressure (ICP), when performed under less than total sterility in animal experiments, may cause significant changes in ICP over a period of several hours (14).

Since statistically significant changes over time in baseline CBF during inhalational anaesthesia may occur over a period of several hours (15, 16), the order of the three drugs in each experiment was randomized.

Cerebral vasoreactivity to hypocapnia

Effects on MAP must be taken into consideration when comparing CBF values obtained under inhalational anaesthesia, since impairment of cerebrovascular autoregulation may occur with high doses of volatile anaesthetic agents (17–19). Since the differences in MAP between normocapnia and hypocapnia were small, the decline in CBF on hyperventilation indicates that none of the agents abolished CO₂-reactivity at either MAC level although hypocapnia was induced after the intended steady-state concentration of inhalational agent had been achieved. In

previous studies, sevoflurane (20, 21) and desflurane (22) have both been reported not to abolish cerebral vasoreactivity to hypocapnia. Sevoflurane has also been found to resemble isoflurane with respect to dose-dependent impairment of hypocapnia-induced cerebral vasoconstriction *in vitro* (7). In contrast to older agents like halothane, isoflurane is known to preserve CO₂-reactivity well enough to enable hyperventilation to reduce the drug-induced cerebral hyperaemia during steady-state exposure to the inhalational agent (23, 24). The present study confirms this finding and also indicates that desflurane and sevoflurane both share this property of isoflurane.

Comparison of CBF at hypocapnia

At hypocapnia, all three agents had similar effects on CBF at lower concentrations. At higher concentrations and hypocapnia, sevoflurane and isoflurane were still similar in their effects on CBF, whereas desflurane was associated with significantly higher CBF. Although MAP was significantly lower with desflurane than with sevoflurane, CBF was still higher with desflurane than with sevoflurane. The present study indicates that the more extensive cerebral vasodilation at normocapnia found to occur with higher doses of desflurane than with equianaesthetic doses of isoflurane or sevoflurane (2) still occurs after hyperventilation.

This more pronounced property of desflurane to increase the cerebral blood volume is in concordance with the findings in a recent study in children (25) where all three agents increased ICP as compared with baseline despite moderate hyperventilation but with a tendency towards higher ICP with desflurane.

Electrocortical activity

Sevoflurane has been reported to cause epileptiform electrocortical activity (26), but in this study none of the studied agents was associated with epileptiform EEG activity. Instead, there was similar dose-dependent suppression of electrocortical activity by all three study drugs with burst-suppression EEG patterns found in all animals exposed to 1.0 MAC of either study drug.

Conclusion

Desflurane and sevoflurane, like isoflurane, do not abolish CO₂-reactivity, and in lower doses they are similar to isoflurane in their cerebral vasodilating effects at hypocapnia. However, in higher doses desflurane induces more vasodilation at hypocapnia than both sevoflurane and isoflurane, which could indicate that desflurane is less suitable for clinical neuroanaesthesia.

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