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# Sevoflurane improves neurological outcome after incomplete cerebral ischaemia in rats

C. WERNER, O. MÖLLENBERG, E. KOCHS AND J. SCHULTE AM ESCH

## Summary

We have studied the effects of sevoflurane on neurological outcome in a rat model of incomplete cerebral ischaemia. After institutional approval, 30 non-fasted male Sprague–Dawley rats (455–555 g) were anaesthetized, the trachea intubated and the lungs ventilated mechanically with isoflurane and 30 % oxygen in air. Catheters were inserted into the right femoral artery, both femoral veins and into the right jugular vein for measurement of arterial pressure, drug administration and blood sampling. At completion of surgery, isoflurane was discontinued and the rats were allowed an equilibration period of 30 min according to the following regimens: group 1 ($n = 10$) received 70 % nitrous oxide in oxygen and fentanyl (bolus 10 $\mu g\,kg^{-1}$ i.v.; infusion 25 $\mu g\,kg^{-1}\,h^{-1}$); group 2 ($n = 10$) received 1.98 vol% sevoflurane in oxygen and air ($F_{I_{O_2}}$ 0.3); group 3 ($n = 10$) received 1.98 vol % sevoflurane in oxygen and air ($F_{I_{O_2}}$ 0.3) and 40 % glucose (6 ml $kg^{-1}$ i.p.) 30 min before ischaemia. Ischaemia was produced by combined unilateral common carotid artery ligation and haemorrhagic hypotension to 35 mm Hg for 30 min. Temperature, arterial blood-gas variables and arterial pH were maintained within the physiological range. Plasma glucose concentration was measured before, during and after ischaemia. Neurological deficit was evaluated for 3 days after ischaemia. Neurological outcome was better in sevoflurane anaesthetized animals, regardless of the plasma glucose concentration, compared with nitrous oxide–fentanyl controls. This indicates that differences in plasma glucose concentrations do not account for the cerebral protection seen with sevoflurane. (*Br. J. Anaesth*. 1995; **75**: 756–760)

**Key words**

Anaesthetics volatile, sevoflurane. Brain, ischaemia. Rat.

Sevoflurane (fluoromethyl-1,1,1,3,3,3-hexa-fluoroisopropyl ether) is a pleasant-smelling volatile anaesthetic with a low blood–gas partition coefficient (0.6) similar to that of nitrous oxide. The non-irritating odour of sevoflurane produces less coughing and straining during induction and emergence and the low blood-gas solubility promotes rapid recovery from anaesthesia. In humans, the anaesthetic potency of sevoflurane (as expressed by the minimum alveolar concentration (1 MAC) with oxygen: 1.71 vol %) is less than that of isoflurane (1 MAC with oxygen: 1.15 vol %). In common with isoflurane, sevoflurane induces dose-related systemic vasodilatation, decreases cardiac output and suppresses the activity of the sympathetic nervous system. Inhalation of sevoflurane is associated with dose-dependent cerebral metabolic depression and EEG burst suppression without evidence of seizure activity, similar to the cerebral metabolic effects of isoflurane [1, 2]. At 1 and 2 MAC of sevoflurane or isoflurane, cerebral blood flow (CBF) remains unchanged or is increased. The cerebrovascular responses to changes in arterial carbon dioxide and CBF autoregulation are maintained with both sevoflurane and isoflurane in concentrations less than 1 MAC [1–4]. During sevoflurane anaesthesia, intracranial pressure remains constant with concomitant hyperventilation [3]. The favourable pharmacokinetic properties and the cerebral metabolic depression associated with minor changes in CBF suggest that sevoflurane may be a suitable anaesthetic for neurosurgical patients. In the present study we have investigated the effects of sevoflurane on neurological outcome in a rat model of incomplete cerebral ischaemia.

## Materials and methods

After approval from the Institutional Animal Care Committee, 30 non-fasted male Sprague–Dawley rats (455–555 g) were anaesthetized in a bell jar with isoflurane, the trachea intubated and the lungs ventilated mechanically with 2 % isoflurane in 30 % oxygen and air. Catheters were inserted into both femoral arteries and veins for continuous arterial pressure measurement, blood sampling and drug administration. A catheter was inserted into the right jugular vein for blood sampling during ischaemia. The right common carotid artery was isolated and a loose ligature placed around the vessel for later

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*Table 1* Mean arterial pressure (MAP); plasma glucose, arterial blood-gas tensions and arterial pH at control, during ischaemia and during recovery (mean (SEM)). ⋆$P < 0.05$ *vs* baseline within group; §$P < 0.05$ *vs* group 1 at each respective treatment

| | Treatment | MAP (mm Hg) | Glucose (mg dl$^{-1}$) | $Pa_{O_2}$ (kPa) | $Pa_{CO_2}$ (kPa) | pH |
|---|---|---|---|---|---|---|
| Group 1 ($n = 10$) | Baseline | 134 (4) | 123 (8) | 18.8 (0.4) | 5.1 (0.1) | 7.42 (0.01) |
| 70 % $N_2O$–fentanyl | 15 min ischaemia | 35 (0.2)⋆ | 330 (16)⋆ | 19.5 (0.7) | 5.6 (0.2)⋆ | 7.38 (0.03)⋆ |
| | 30 min ischaemia | 35 (0.2)⋆ | 255 (28)⋆ | 19.7 (0.5) | 5.4 (0.2) | 7.37 (0.01)⋆ |
| | Recovery | 121 (5) | 97 (3) | 18.9 (0.5) | 5.2 (0.1) | 7.44 (0.01) |
| Group 2 ($n = 10$) | Baseline | 89 (6)§ | 160 (8) | 18.8 (0.5) | 5.1 (0.1) | 7.45 (0.01) |
| 1 MAC sevoflurane | 15 min ischaemia | 35 (0.2)⋆ | 225 (10)⋆§ | 18.7 (0.5) | 5.5 (0.1)⋆ | 7.39 (0.01)⋆ |
| | 30 min ischaemia | 35 (0.2)⋆ | 187 (9)§ | 18.8 (0.7) | 5.3 (0.1) | 7.43 (0.01) |
| | Recovery | 134 (3)⋆§ | 113 (5)⋆ | 17.3 (0.4) | 5.4 (0.1) | 7.46 (0.01) |
| Group 3 ($n = 10$) | Baseline | 74 (7)§ | 304 (19) | 20.1 (0.7) | 5.0 (0.1) | 7.43 (0.01) |
| 1 MAC sevoflurane | 15 min ischaemia | 35 (0.2)⋆ | 273 (18) | 20.5 (0.8) | 5.2 (0.1) | 7.38 (0.01)⋆ |
| + glucose | 30 min ischaemia | 35 (0.2)⋆ | 240 (16)⋆ | 20.7 (0.8) | 5.2 (0.1) | 7.36 (0.01)⋆ |
| | Recovery | 119 (4)⋆ | 171 (17)⋆§ | 20.3 (0.5) | 5.0 (0.1) | 7.43 (0.01) |

clamping. Vecuronium was given as a continuous infusion (0.1 mg kg$^{-1}$ min$^{-1}$) to maintain paralysis. After completion of surgery, the incisions were infiltrated with 0.25 % bupivacaine. Isoflurane was then removed from the inspiratory gas mixture and the animals were allowed an equilibration period of 30 min according to one of the following treatments: rats in group 1 ($n = 10$) received 70 % nitrous oxide in oxygen and fentanyl (bolus 10 g kg$^{-1}$ i. v.; infusion 25 g kg$^{-1}$ h$^{-1}$); rats in group 2 ($n = 10$) received 1 MAC of sevoflurane (1.98 vol% inspired concentration) in oxygen and air ($FI_{O_2}$ 0.3); rats in group 3 ($n = 10$) received 1 MAC of sevoflurane in oxygen and air ($FI_{O_2}$ 0.3) with 40 % glucose (6 ml kg$^{-1}$ i.p.) 30 min before ischaemia.

Cerebral ischaemia was produced by the combination of right common carotid occlusion and haemorrhagic hypotension to a level of 35 mm Hg for 30 min. A range of 1 mm Hg was allowed for target pressure. After 30 min of ischaemia, the carotid artery was unclamped and the withdrawn blood reinfused for 10 min. Rectal temperature was measured using a Yellow Springs thermistor probe and was maintained constant at 37 °C by Servocontrol using an overhead heat lamp. Temperature was controlled during the entire experiment and for a period of 2 h after the animals were returned to their cages. Mechanical ventilation was adjusted to maintain $Pa_{CO_2}$ at 5.1–5.4 kPa. Arterial pH was maintained at normal levels by infusion of bicarbonate. Arterial blood-gas tensions and plasma glucose analyses were performed at baseline, during ischaemia and 15 min after reperfusion. Administration of nitrous oxide–fentanyl (group 1) or sevoflurane (groups 2 and 3) was discontinued 30 min after reperfusion. During recovery, the catheters were removed and the incisions closed. The trachea was then extubated and the rats transferred to their cages.

Neurological outcome scores were evaluated by an investigator blinded to the treatment conditions every 24 h for a period of 3 days, starting 24 h after ischaemia. For the neurological examination, a score of "0" represented no detectable neurological deficit and a score of "17" represented stroke-related death [5]. Stroke-related death was determined a minimum of 3 h after extubation only if the rat showed progressive signs of stroke impairment.

Data are reported as mean (SEM). Neurological deficit score was analysed using the *H* test of Kruskal–Wallis. Physiological variables were analysed using Friedman's test and the Wilcoxon–Wilcox analysis for *post hoc* comparison of differences within groups. The *H* test of Kruskal–Wallis and Harter's test were used for *post hoc* comparison between groups. Significance was assumed at $P < 0.05$.

## Results

Table 1 shows mean arterial pressure (MAP), plasma glucose concentrations, arterial blood-gas tensions and arterial pH before, during and after incomplete cerebral ischaemia. Sevoflurane produced a 36–45 % decrease in MAP before induction of ischaemia compared with nitrous oxide–fentanyl. According to the study design, MAP was decreased to 35 mm Hg in all groups during ischaemia. Post-ischaemic MAP was higher in group 2 (sevoflurane) compared with groups 1 (nitrous oxide–fentanyl) and 3 (glucose-loaded sevoflurane). Plasma glucose concentration increased significantly during ischaemia in all animals but was lower in sevoflurane-anaesthetized rats (group 2) compared with nitrous oxide–fentanyl-anaesthetized (group 1) or glucose-loaded sevoflurane-anaesthetized rats (group 3). Arterial blood-gas tensions and pH did not differ between groups and remained within the physiological range over time.

In nitrous oxide–fentanyl anaesthetized rats (group 1), ischaemia produced stroke-related death in 18 % of animals on day 1, 55 % on day 2 and 64 % on day 3. Neurological deficit was moderate to severe in all other anaesthetized rats (fig. 1). In sevoflurane-anaesthetized rats (group 2), all animals survived the ischaemic challenge with only moderate or minor neurological deficits. In sevoflurane-anaesthetized, glucose-loaded rats (group 3), 20 % of the animals were dead after 3 days while all other animals survived the ischaemic challenge with only minor neurological deficits. Neurological deficit scores were significantly less with sevoflurane regardless of the

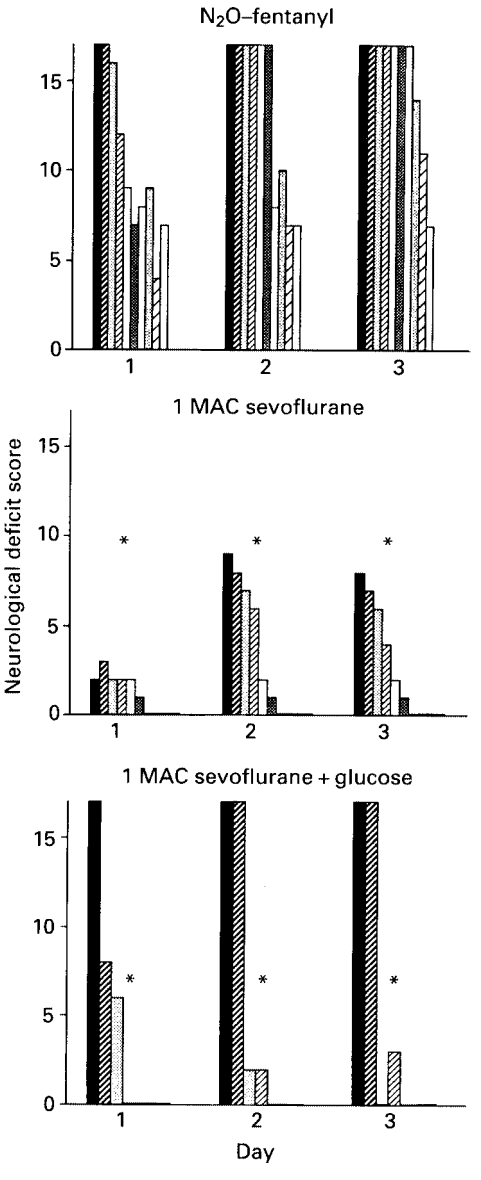


*Figure 1* Neurological deficit scores after incomplete cerebral ischaemia in groups 1, 2 and 3 over a 3-day examination period. A score of "0" represents no neurological deficit, "17" indicates stroke-related death. Sevoflurane anaesthesia was associated with a reduction in neurological deficit regardless of the level of plasma glucose concentration ($*P < 0.05$ *vs* nitrous oxide–fentanyl group).

plasma glucose concentration compared with nitrous oxide–fentanyl controls.

## Discussion

We have found that anaesthesia with sevoflurane improved neurological outcome after experimental incomplete cerebral ischaemia regardless of the level of plasma glucose concentration. The improved outcome could not be explained by differences in body temperature, arterial blood-gas tensions or arterial pH, which were maintained at physiological levels during the study. These results show that decreases in plasma glucose concentration are not a major factor in the reduction of ischaemic brain injury produced by sevoflurane.

The mechanisms by which volatile anaesthetic agents potentially protect the brain are still unclear. Sevoflurane, in common with barbiturates or isoflurane, produces a dose-dependent decrease in cerebral metabolism to an end-point of EEG burst suppression [1,2,6]. Cerebral protection with these anaesthetics has been explained by a reduction in cerebral metabolic requirements, thus counterbalancing the diminished oxygen–substrate delivery, provided some neuronal activity is preserved. Previous studies using the present model of incomplete hemispheric ischaemia have shown persisting neuronal activity during the ischaemic insult [7]. Thus it is possible that the present model provides a cerebral functional state which is sensitive to anaesthetic protection compared with models with a more severe ischaemic insult that renders the EEG isoelectric [7, 8]. However, cerebral functional and metabolic suppression has been questioned as a major mechanism of neuronal protection because observations in laboratory animals have shown profound protection with mild hypothermia (a state of only minor suppression of EEG activity and cerebral metabolism) [9]. In contrast, administration of hypnotics, halothane or isoflurane was associated with only moderate or no cerebral protection despite substantial suppression of the EEG and cerebral metabolism [10]. This suggests that cerebral metabolic suppression with anaesthetics is of limited relevance in the concept of neuronal protection.

Incomplete hemispheric ischaemia appears to be sensitive to reductions in peripheral and central sympathetic tone. Studies using the present ischaemia model have shown that infusion of the ganglionic blocking agent hexamethonium or the $\alpha_2$ adrenergic agonist dexmedetomidine was associated with reductions in neurological deficit [11,12]. This is consistent with the observation that improved outcome after halothane or isoflurane anaesthesia was related closely to decreases in central and peripheral catecholamine concentrations [5,13]. Although excitatory neurotransmitter release .was not measured during the present study it is possible that cerebral protection with sevoflurane is a function of decreased catecholamine turnover.

Increased plasma concentrations of glucose protect the brain from energy state depletion but worsen long-term ischaemic neuronal damage and neurological outcome [14]. In the present experiments, intra-ischaemic plasma glucose concentrations were lower in sevoflurane-anaesthetized rats compared with nitrous oxide–fentanyl controls. This may have improved neurological outcome with sevoflurane. However, the protective effect of sevoflurane was not reversed by artificial elevation of plasma glucose concentration in a third group of animals. This indicates that improvement in neurological outcome after sevoflurane was not related to reductions in intra-ischaemic plasma glucose concentrations.

The results of experiments testing neurological outcome after cerebral ischaemia are critically dependent on the background anaesthetic treatment in the control group. Studies in rats and primates subjected to focal or near-complete forebrain ischaemia have shown that isoflurane anaesthesia

was not associated with improved neurological or histopathological outcome compared with halothane or barbiturates [9, 10, 15, 16]. In contrast, the present experiments and studies in isoflurane- or sevoflurane-anaesthetized rats have shown reductions in stroke-related mortality, neurological deficit and infarct size after incomplete hemispheric or focal ischaemia compared with lightly anaesthetized or awake controls [5, 7, 17, 18]. This suggests that the protective potential of isoflurane is masked when comparing this agent with halothane- or barbiturate-anaesthetized controls (i.e. agents with a protective potency *per se*). In contrast, cerebral protection becomes evident when comparing isoflurane with awake or nitrous oxide–fentanyl-anaesthetized controls in the same models. This suggests that experimental neuronal protection is related to the presence or absence of background anaesthetics and the status of neuronal activity in control animals. During the present study, the combination of 70 % nitrous oxide in oxygen and fentanyl (bolus 10 $\mu g\ kg^{-1}$ i.v.; infusion 25 $\mu g\ kg^{-1}\ h^{-1}$) was used as the control background anaesthetic treatment. This decision was based on previous experiments showing similar levels of cerebral and spinal cord blood flow in awake compared with nitrous oxide–fentanyl-anaesthetized animals [19]. Additionally, CBF autoregulation did not differ between the awake and anaesthetized state. These results are consistent with experiments in rats undergoing ventilation with nitrous oxide where infusion of fentanyl 25 $\mu g\ kg^{-1}$ did not change cerebral oxygen consumption compared with nitrous oxide alone [20]. This supports the concept of the use of nitrous oxide–fentanyl anaesthesia as an appropriate control anaesthetic treatment as this produces levels of CBF and cerebral metabolism close to those of the awake rat.

One confounding factor in the present experiment is the measurement and maintenance of rectal temperature rather than pericranial or brain temperature at 37 °C. Because of the invasive nature of pericranial or brain temperature probes, rectal temperature was controlled to provide comparable temperature levels even during the recovery period after the extubated rats were returned to their cages. This is based on observations showing substantial protection with post-ischaemic mild hypothermia [21, 22]. Additionally, experiments in gerbils have shown that changes in pericranial temperature closely reflect rectal temperature during complete transient forebrain ischaemia [23, 24]. As measurement and control of body temperature were performed in an identical fashion in all animals, it is unlikely that differences in brain temperature account for the differences in outcome.

The amount of blood withdrawn to induce haemorrhagic hypotension was higher in control animals (16.0 (0.6) ml) compared with sevoflurane-anaesthetized normoglycaemic (10.2 (0.8) ml) or hyperglycaemic rats (7.1 (0.5) ml). Differences in total blood volume during ischaemia may have influenced cardiac output and CBF. However, studies in animals and patients with brain injury suggest that changes in cardiac output have no clinically relevant impact on CBF [25, 26]. It is unlikely therefore that transient differences in total blood volume are a major factor in differences in neurological outcome.

We conclude that sevoflurane, improved neurological outcome after incomplete cerebral ischaemia in rats compared with animals anaesthetized with nitrous oxide–fentanyl, regardless of plasma glucose concentrations. Hypothetical mechanisms include suppression of the level of cerebral excitation caused by anaesthetic deafferentiation and decreases in central and peripheral catecholamine turnover. However, the results of this study need to be interpreted with caution if applied to humans. Sevoflurane is a cerebral and systemic vasodilator with the potential to decrease cerebral perfusion pressure by lowering arterial pressure and increasing intracranial pressure. Thus sevoflurane may not be indicated in neurosurgical patients with intracranial mass lesions and reduced craniospinal compliance.

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