Sevoflurane induces less cerebral vasodilation than isoflurane at the same A-line autoregressive index level.

Holmström, Anders; Åkeson, Jonas

Published in:
Acta Anaesthesiologica Scandinavica

DOI:
10.1111/j.1399-6576.2004.00576.x

2005

Acta Anaesthesiol Scand 2005; 49: 16–22
Printed in Denmark. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2004.00576.x

Sevoflurane induces less cerebral vasodilation than isoflurane at the same A-line® autoregressive index level

A. HOLMSTRÖM and J. ÅKESON
Department of Anesthesia and Intensive Care, Malmö University Hospital, Lund University, Malmö, Sweden

Background: The use of sevoflurane in neuroanesthesia is still under debate. Comparison of dose-dependent vasodilatory properties between sevoflurane and isoflurane, the more traditional neuroanesthetic agent, requires comparable dosing of the agents. A-line® autoregressive index (AAI) provides reproducible individual measurement of anesthetic depth.
Methods: Sevoflurane and isoflurane, in randomized order, were titrated to a stable AAI of 15–20 in each of 18 ASA I or II patients. The mean flow velocity (Vmca) and pulsatility index (PI) in the middle cerebral artery were measured with transcranial Doppler at an end-tidal CO_2 of 4.5%.
Results: For sevoflurane Vmca was 18% lower [95% confidence interval (CI) 12–22%; $P < 0.00001$] and PI was 23% higher (95% CI 12–33%; $P = 0.0013$) than for isoflurane. Mean arterial blood pressure did not differ between the two agents. The minimum alveolar concentration (MAC) fraction necessary to reach the intended AAI level was 13% higher (95% CI 5–20%; $P = 0.0079$) with sevoflurane than with isoflurane.
Conclusion: Sevoflurane induced less cerebral vasodilation than isoflurane at the same depth of anesthesia, measured by AAI, and hence seems more favorable for clinical neuroanesthesia. In our opinion the difference between sevoflurane and isoflurane in the MAC fraction required to attain the same AAI level demonstrates the limitations of MAC in defining the level of anesthesia.

Accepted for publication 7 September 2004

Key words: AAI; anesthesia; auditory evoked potentials; cerebral blood flow; isoflurane; MAC; minimum alveolar concentration; sevoflurane; transcranial Doppler.

THE possible usefulness of sevoflurane in clinical neuroanesthesia is still under investigation (1, 2). Sevoflurane has been found to enable faster recovery and faster postoperative neurological assessment than isoflurane in neurosurgical patients, thereby enabling earlier detection of postoperative intracranial complications (3). Recent studies have shown that sevoflurane has less direct cerebral vasodilatory properties in humans (4) and less total cerebral vasodilatory properties in animals (2) than isoflurane, the more traditional inhalational agent in neuroanesthesia, and might therefore affect intracranial pressure (ICP) less than isoflurane. However, it has previously not been shown that sevoflurane has less total cerebral vasodilatory effects than isoflurane in humans.

Inhalational agents must be studied at equipotent levels of anesthesia for reliable comparison of their dose-dependent effects (5). The most common way of describing the anesthetic potency of an inhalational agent is by its minimum alveolar concentration (MAC), but MAC values differ between studies depending on the method used and on the age and size of the subjects (5, 6). Neurophysiological techniques for assessment of anesthetic depth, such as the A-Line® (Alaris Medical Systems Inc, San Diego, CA) auditory evoked potentials (AEP) monitor, offer an objective way of attaining an equipotent level of anesthesia for comparison of dose-dependent side-effects of inhalational anesthetic agents (7, 8).

The primary aim of the present randomized controlled clinical trial was to compare the cerebral vasodilatory properties of sevoflurane and isoflurane by transcranial Doppler measurements at equipotent anesthesia as indicated by the A-Line® autoregressive index (AAI). The secondary aim was to compare sevoflurane and isoflurane with respect to the MAC fraction required to attain the intended AAI level.

Patients and methods

The study protocol was approved by the Research Ethics Committee of the Medical Faculty at Lund

University, Lund, Sweden, and of the Medical Products Agency in Uppsala, Sweden.

Twenty ASA I or II patients, aged 20–72 years, scheduled for elective orthopedic procedures in the lower limb including use of a lower limb tourniquet, were recruited for the study. Patients with known hearing problems were not recruited. Before signing a written consent to participate in the study, all patients received both oral and written information. Randomization of the order of the two agents in the patients was done with sealed envelopes – 10 with the agents in the order isoflurane/sevoflurane and 10 with the order sevoflurane/isoflurane. Two patients were excluded due to lack of an acoustic window for the Doppler measurements but the remaining 18 patients all had a complete set of measurements. The two excluded patients both had sevoflurane as the first agent and consequently, in the included patients, isoflurane was the first agent in 10 patients and sevoflurane was the first agent in eight patients. The group consisted of eight males and 10 females aged 51 ± 14 years and with weight 80 ± 12 kg. Seven patients were ASA I and 11 were ASA II. Peroperative bleeding did not exceed 50 ml.

Oral premedication was given with 1 g paracetamol (Panodil®, GlaxoSmithKline, Mölndal, Sweden). Glycopyrron (Robinul®, Meda AB, Solna, Sweden) 5 $\mu g \cdot kg^{-1}$ and remifentanil (Ultiva®, GlaxoSmithKline) 0.5 $\mu g \cdot kg^{-1}$ was given intravenously (iv) before an iv infusion of remifentanil was started at a rate of 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After preoxygenation, anesthesia was induced with propofol (Propofol Lipuro®, B. Braun, Melsungen, Germany) iv in sufficient dose until loss of eyelash reflex (2.7 ± 0.5 $mg \cdot kg^{-1}$; mean ± SD), and succinylcholine (Celocurin®, IPEX Medical AB, Solna, Sweden) iv 1.5 $mg \cdot kg^{-1}$ was given to facilitate endotracheal intubation. The patients then received sevoflurane and isoflurane in the predetermined randomized order. The flow of oxygen in air mixture into the anesthesia circuit was set to 6 $l\,min^{-1}$, with the inspired oxygen content (FiO_2) 0.3–0.4 with the same FiO_2 at both measure points in each individual patient. Sevoflurane and isoflurane were administered with Penlon vaporizers (Penlon®, Swindon, UK).

A Viridia® Anesthesia Monitor (Agilent Technologies®, Englewood, CO) was used for the monitoring of EKG, SpO_2 and non-invasive blood pressure. The cuff for non-invasive blood pressure was fitted to an upper arm according to the manufacturer's instructions and was not moved during the operation. Inspiratory and expiratory gas concentrations were monitored with a Capnomac Ultima® agent monitor (Datex®, Helsinki, Finland), calibrated before the experimental procedures by the Department of Medical Technology, Malmö University Hospital.

After induction of anesthesia, three silver/silver chloride electrodes (A-Line®, Danmeter® AS, Odense, Denmark) were placed according to the instructions from the manufacturer of the A-Line® AEP Monitor 2 after site skin preparation (Red Dot Trace Prep®, 3M®, St. Paul, MN) – the positive electrode at the median forehead, the negative electrode at the left mastoid and the reference electrode at the left forehead. Electrode impedance was maintained at less than 5 kΩ. Headphones gave bilateral click sound stimuli with 2-ms duration and 9-Hz repetition rate with the intensity automatically adjusted to 45–75 dB according to signal quality. The AEP signals were continuously recorded with an A-Line® AEP Monitor 2. Mid-latency 40-Hz AEP signals were extracted from the EEG by autoregression with exogenous input modeling (9, 10) – AAI version 4.2 with software version 1.61 (Danmeter® AS, Odense, Denmark). This version of AAI is a combination of AEP and EEG, where the emphasis is on AEP with a contribution of EEG when the AEP signal is insufficient. At all measure points in the present study, the monitoring device indicated the AEP signal to be sufficient for calculation of AAI and also indicated an adequate signal-to-noise ratio.

At least 30 min after induction and at least 15 min after skin incision, the dose of the inhalational agent was titrated to attain a stable AAI between 15 and 20, together with a stable end-tidal concentration of inhalational agent for at least 5 min before Doppler measurements were made.

The blood flow velocities in the middle cerebral artery (MCA) were measured at both measure points using pulsed 2-MHz transcranial Doppler ultrasound equipment (TC2–64B, EME®, Überlingen, Germany). This ultrasound device operates with a maximum intensity of 100 $mW \cdot cm^{-2}$ and pulse repetition frequencies between 4.96 and 20.52 kHz. Bidirectional signals were recorded with a 10-kHz low-pass filter and a 150-Hz high-pass filter. The Doppler probe was placed in the temporal region at the site where the best signal was found. The probe was not fixed since intermittent movement of the patient occurred during the study period due to the surgical procedures. Transcranial Doppler ultrasound signals of the MCA were obtained at a depth of 45–55 mm (48 ± 5 mm; mean ±SD). The instrument computed the time-mean MCA flow velocity (Vmca) using a fast-Fourier

real-time frequency analysis. The pulsatility index (PI) was computed according to the formula:

$$\mathrm{PI} = \frac{(\text{systolic flow velocity} - \text{diastolic flow velocity})}{\mathrm{Vmca}}. \quad (11)$$

Once a clearly readable waveform was obtained, Vmca and PI data were recorded together with corresponding AAI, gas concentrations, hemodynamic data and tympanic temperature (First Temp Genius®, Sherwood Medical, Sussex, UK). The examiner was not blinded to which agent was investigated when the Doppler measurements were performed.

After finishing measurements with the first agent, the inhalational agent was switched according to randomization and the fresh gas flow into the anesthesia circuit was increased to $12\,l\,min^{-1}$ for 30 min to wash out the previous agent before the measurement procedures were repeated with the second agent.

Ventilation was always adjusted to obtain the same end-tidal concentrations of carbon dioxide ($ETCO_2$ 4.5%) for the two compared agents at the corresponding measure points. The mean arterial pressure (MAP) was at least 50 mmHg at all measure points. All patients were supine without elevation or lowering of the head.

To compare the MAC fractions of sevoflurane or isoflurane required to achieve the intended AAI level, an age-adjusted MAC value was calculated for each agent in each patient by the Mapleson method (6) on study completion.

Statistical methods

Power analysis showed that 20 patients would be needed to detect a 10% difference between the study drugs with a power of 80%, a probability of 95% and a case dropout rate of 10%. After normal distribution had been verified, a paired *t*-test was used for comparison between the two measure points, and linear regression analysis was used for correlation of cerebral data to age. Carry-over effects and order-effect relations were tested by a two-sample *t*-test. 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). Demographic and physiological data are presented as mean ± SD, calculated differences as mean with 95% confidence interval (CI) and regression coefficients (R) with 95% CI in the text and Tables 1 and 2.

Results

Temperature at the Doppler measurements was for sevoflurane 36.5 ± 0.3 and for isoflurane 36.5 ± 0.2. Temperature at the measurements with the first agent in each patient was 36.6 ± 0.2 and at the measurements with the second agent 36.5 ± 0.2.

There were no differences in AAI level between the study drugs (Table 1).

Values for sevoflurane when administered as first agent were for Vmca $41 \pm 7\,cm\,s^{-1}$, for PI 0.9 ± 0.2 and for the fraction of age-adjusted MAC required to reach the intended AAI level (frMAC) 1.0 ± 0.2, and values when administered as second agent were for Vmca $41 \pm 10\,cm\,s^{-1}$, for PI 1.0 ± 0.2 and for frMAC 0.9 ± 0.3. Values for isoflurane as first agent were for Vmca $47 \pm 13\,cm\,s^{-1}$, for PI 0.8 ± 0.3 and for frMAC 0.8 ± 0.3, and values when occurring as second agent were for Vmca $52 \pm 8\,cm\,s^{-1}$, for PI 0.7 ± 0.3 and for frMAC 0.9 ± 0.2. No carry-over effect due to the order of agents was found for Vmca, PI or frMAC, since the respective CI for carry-over effects included zero (for Vmca −25–13 $cm\,s^{-1}$; for PI −0.20–0.67; for frMAC −0.86–0.12). No order-effect relations were found for Vmca, PI or frMAC since the respective CI for order-effects included zero (for Vmca −4.2–0.9 $cm\,s^{-1}$; for PI −0.08–0.09; for frMAC −0.05–0.13).

Table 1

Electrophysiological variables and concentrations of inhalational agent (mean ± SD) in 18 patients sequentially exposed to sevoflurane and isoflurane in randomized order.

	Sevoflurane	Isoflurane	Sevoflurane–isoflurane (95 % confidence interval) Absolute difference	Relative difference (%)	*P*-value
A-Line autoregressive index (AAI)	18 ± 2	17 ± 1	1 (−2–0)	–	0.86
Fraction of age-adjusted minimum alveolar concentration at the intended AAI level	0.97 ± 0.26 (0.47–1.42)	0.86 ± 0.25 (0.45–1.46)	0.11 (0.04–0.17)	13 (5–20)	
End-tidal alveolar agent concentration (%)	1.9 ± 0.5 (0.9–2.7)	1.1 ± 0.3 (0.6–1.8)	–	–	0.0079 –

Differences between study drugs are reported as mean with 95 % confidence interval.

Table 2

Cerebral hemodynamic data (mean ± SD) obtained in 18 patients sequentially exposed to sevoflurane and isoflurane in randomized order.

	Sevoflurane	Isoflurane	Sevoflurane–isoflurane (95 % confidence interval) Absolute difference	Relative difference (%)	*P*-value
Mean flow velocity in the middle cerebral artery ($cm \cdot s^{-1}$)	40 ± 8	49 ± 11	−9 (−11 to −6)	−18 (−22 to −12)	<0.00001
Pulsatility index in the middle cerebral artery	0.96 ± 0.20	0.78 ± 0.26	0.18 (0.09–0.26)	23 (12–33)	0.0013

Differences between study drugs are reported as mean with 95 % confidence interval.

The frMAC was found to be 13% higher (CI 5–20%; $P = 0.0079$) for sevoflurane than for isoflurane (Table 1).

For sevoflurane, the Vmca was 18% lower (CI 12–22%; $P < 0.00001$) and PI was 23% higher (CI 12–33%; $P = 0.0013$) than with isoflurane (Table 2). MAP was the same for both agents: 66 ± 10 mmHg (range for sevoflurane 52–85 mmHg and range for isoflurane 51–86 mmHg). End-tidal concentration of CO_2 was also the same for both agents: 4.4 ± 0.1%. Vmca decreased significantly with age for isoflurane [$R = -0.41$ (CI −0.76–−0.06; $P = 0.025$)] but not for sevoflurane [$R = -0.26$ (CI −0.54–0.03; $P = 0.076$)], whereas PI increased significantly with age for both sevoflurane [$R = 0.008$ (CI 0.002–0.014; $P = 0.011$)] and isoflurane [$R = 0.013$ (CI 0.005–0.020; $P = 0.003$)] (Fig. 1). The relative difference in Vmca between sevoflurane and isoflurane did not change significantly with age [$R = -0.36$ (CI −0.71–0.11; $P = 0.138$)], whereas the relative difference in PI did [$R = 0.47$ (CI 0.014–1.89; $P = 0.047$)].

Discussion

Stability of the present model

Since temperature was stable over time and since there were no order-effects in the studied data, it is unlikely that significant change over time in background factors such as baseline cerebral metabolism occurred to the degree that it would affect the study results.

AAI for titration of equi-anesthetic doses of sevoflurane and isoflurane

In the present study, a higher MAC fraction of sevoflurane than isoflurane was required to achieve the same AAI. Since the cerebral vasodilatory side-effects of inhalational agents are dose-dependent, reliable comparisons between agents regarding their cerebral vasodilatory properties must be made at equal levels of anesthesia (5). MAC is often used to define the potency of an inhalational agent, but the determination of MAC is influenced by the method, age and size of the exposed individual and the method as such is associated with highly biased underestimates of variability (5, 12, 13). Consequently, the depth of anesthesia resulting from exposure to 1.0 MAC of one inhalational agent may differ from the exposure to 1.0 MAC of another inhalational agent in the same individual. Since studies in rats have shown that decapitation does not change the MAC value of an inhalational agent (14), it might be questioned if MAC is an appropriate reference for comparison of cerebral effects and side-effects between inhalational agents. Apart from these problems, MAC only approximates the anesthetic potency of an inhalational agent in a group of individuals, and does not necessarily reflect the resulting depth of anesthesia in each individual. Objective neurophysiological methods, such as AAI, reflect individual depth of anesthesia in humans (8) and might therefore provide more exact rationales for comparison of dose-dependent side-effects of inhalational agents.

The AAI has been reported to correlate with the depth of both sevoflurane (10) and isoflurane (15) anesthesia. Early AAI prototypes had problems in showing graded responses in AAI during exposure to varying end-tidal steady-state concentrations of inhalational agent, probably due to problems with high electrode impedance and electromyographic (EMG) disturbances (9). The modern monitor used in the present study monitored electrode impedance and EMG and was capable of providing graded responses in AAI also to small changes in end-tidal agent concentrations.

In the algorithm behind AAI, the level of influence of the used anesthetic on AEP is indexed to 100 when the patient is awake and to 25–30 at an anesthetic depth enough to abolish a reaction to skin incision

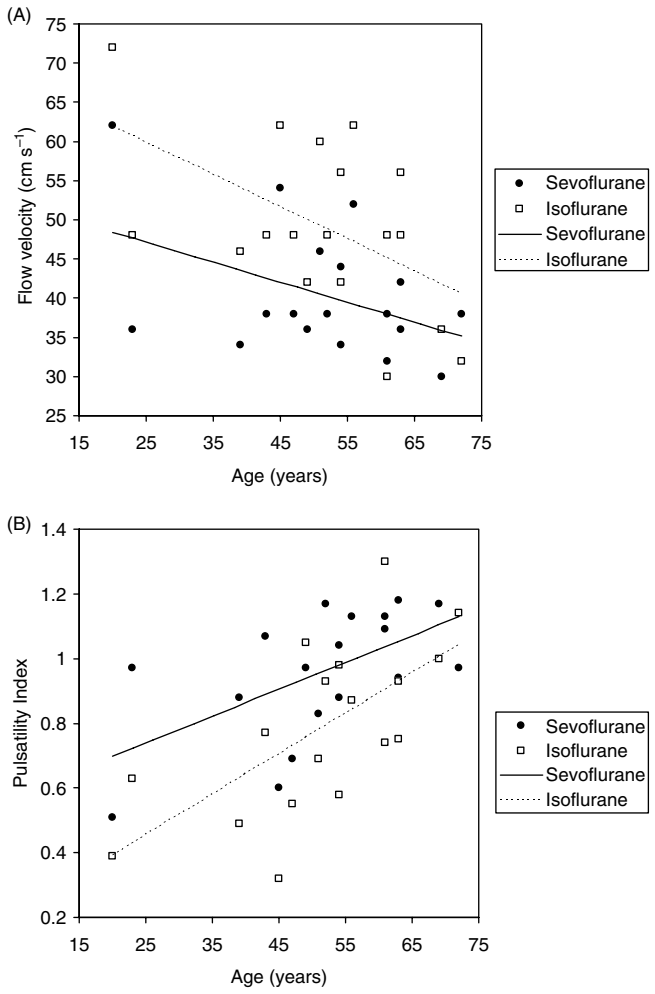

Fig. 1. Values on mean flow velocity (A) and pulsatility index (B) in the middle cerebral artery for the two inhalational agents sevoflurane and isoflurane in each individual patient (n=18).

(15, 16). The AAI level for surgical anesthesia recommended by the manufacturer is 15–25 and in the present study the AAI level was titrated to 15–20, since less variability in response to surgical stimulation seemed to occur in this interval than in the interval 20–25.

Depth-of-anesthesia monitors have been suggested to reflect the level of hypnosis rather than the level of clinical anesthesia in all its complex aspects (8). In the present study, this is of minor importance, since the AAI level would still similarly reflect the effects of the two study drugs even if the major effects measured were the hypnotic effects of the respective agent.

Since an inhalational agent is often combined with an opioid in neuroanesthesia, a stable background of opioid would be desirable when comparing cerebrovascular effects of inhalational agents. Remifentanil has been the opioid of choice in several studies on AAI and can be presumed to influence AAI similarly with both study drugs in the present study (17).

Several different MAC-values for both sevoflurane and isoflurane in man have been published and to increase the accuracy of MAC by considering age, Mapleson made age-adjustments of existing MAC-values for sevoflurane and isoflurane in a meta-analysis (6). This method has recently been used in scientific studies involving MAC (4). Despite individual age-adjustments of MAC in the present study, higher MAC fractions of sevoflurane than of isoflurane were required to achieve the same AAI level. Since AAI can be considered to reflect the level of anesthesia and since sevoflurane and isoflurane can be expected to affect AAI in the same way, 1.0 MAC of sevoflurane consequently resulted in lighter anesthesia than did 1.0 MAC of isoflurane. Also, both agents showed considerable and similar inter-individual variation in the age-adjusted MAC fraction needed for the intended AAI level. This demonstrates the limitations of MAC in defining the individual level of anesthesia and that the use of MAC for the comparisons of two different inhalational agents in the same individual could result in a difference in anesthetic depth between the compared agents.

Cerebral vasodilatory effects of sevoflurane compared to those of isoflurane

Lower Vmca and higher PI were found with sevoflurane than with isoflurane at the same level of AAI in the present study. Although an error may have been introduced into the measurements, since the examiner was unblinded, it is unlikely that this would be the reason for the differences in Vmca and PI between the study drugs since the study procedures were highly standardized and the ultrasound probe was positioned to achieve maximal signal regardless of the study drug. Changes in Vmca reliably correlate with changes in cerebral blood flow (CBF) although flow velocity cannot be used as a measure of CBF (18). Pulsatility index (PI) is a measure of vascular resistance when determining flow velocity with Doppler (11) and is considered to provide a reliable estimation of the cerebrovascular resistance also during inhalational anesthesia (19). Intraindividual differences in Vmca and PI between sevoflurane and isoflurane in the present study can consequently be considered to reflect true differences in vasodilatory effects.

Although isoflurane has a higher blood/gas partition coefficient than sevoflurane, the order of agents in the present study did not significantly influence the results, since no carry-over effects or order-related

effects occurred. This is in concordance with a large study (20) on 2008 patients given either sevoflurane or isoflurane where there were no differences in time to emergence and in time to orientation between the two agents as long as the time of exposure to the agent did not exceed 1 h. In the present study the first agent was always administered for less than 1 h before the washout period of 30 min between the agents. The washout period in the present study was fourfold the time needed for emergence and more than threefold the time needed for orientation (20).

Cerebral vasodilatory effects of inhalational agents should be compared at similar MAP levels, since inhalational agents dose-dependently impair cerebral autoregulation (21). There was no difference in effect on MAP between the two study drugs, so the observed differences in variables reflecting cerebral vasodilation did not result from different systemic hemodynamic depression by the study drugs.

One study using transcranial Doppler in humans (4) has found sevoflurane to have less direct vasodilating effects than isoflurane when possible influences of indirect vasoconstriction due to differences in neuroexcitation (22) had been suppressed by simultaneous induction of EEG silence with propofol. Other unpaired studies using transcranial Doppler in humans but no metabolic depression with a separate anesthetic drug found only a non-significant tendency towards differences in total cerebral vasodilatory effects between sevoflurane and isoflurane – possibly due to lack of statistical power since only six to eight patients were included for each agent (21, 23). In a recent animal study with experimentally increased ICP and without metabolic suppression by a separate drug, sevoflurane was associated with less cerebral vasodilation and lower ICP than an equipotent dose of isoflurane (5). According to the present study's finding that 1.0 MAC of sevoflurane resulted in lighter anesthesia than did 1.0 MAC of isoflurane, previous Doppler studies using MAC as the definition of anesthetic depth (4, 21, 23) were made at lighter anesthesia with sevoflurane than with isoflurane, which actually should have resulted in larger differences in dose-dependent cerebral vasodilation than in the present study. The main reason for the present study's statistically significant differences in total cerebral vasodilatory properties between sevoflurane and isoflurane was most probably the presence of adequate statistical power and not the method of defining the depth of anesthesia.

Normally without anesthesia, Vmca decreases and PI increases with age due to decreasing vascular compliance with increasing age (24). This also seems to be the case under inhalational anesthesia since similar changes with age were found for PI with both agents and for Vmca with isoflurane, whereas the change with age in Vmca with sevoflurane did not reach statistical significance. Also, the relative differences between sevoflurane and isoflurane in effects on PI decreased significantly with age, whereas the corresponding differences in effects on Vmca did not. Since PI probably better reflects cerebrovascular resistance than does Vmca (11), this implies that the clinical benefits of less cerebral vasodilation resulting from choosing sevoflurane instead of isoflurane for neuroanesthesia might decrease with increasing age.

Conclusion

Sevoflurane had less total cerebral vasodilatory effects than isoflurane at the same depth of anesthesia, according to the AAI level, in the present randomized, controlled clinical study. This indicates that sevoflurane in humans might be less likely than isoflurane to increase an already raised ICP to possibly dangerous levels by increasing cerebral blood volume. In our opinion the difference between sevoflurane and isoflurane in the MAC fraction required to attain the same AAI level demonstrates the limitations of MAC in defining the level of anesthesia.

References

1. Sponheim S, Skraastad Ø, Helseth E, Due-Tønnesen B et al. Effects of 0.5 and 1.0 MAC isoflurane, sevoflurane and desflurane on intracranial and cerebral perfusion pressures in children. *Acta Anaesthesiol Scand* 2003; **47**: 932–8.
2. Holmström A, Åkeson J. Desflurane increases ICP more and sevoflurane less than isoflurane in pigs subjected to intracranial hypertension. *J Neurosurg Anesthesiol* 2004; **16**: 136–43.
3. Gauthier A, Girard F, Boudreault D, Ruel M et al. Sevoflurane provides faster recovery and postoperative neurological assessment than isoflurane in long-duration neurosurgical cases. *Anesth Analg* 2002; **95**: 1384–8.
4. Matta BF, Heath KJ, Tipping K, Summors AC. Direct cerebral vasodilatory effects of sevoflurane and isoflurane. *Anesthesiology* 1999; **91**: 677–80.
5. Holmström A, Åkeson J. Cerebral blood flow at 0.5 and 1.0 minimal alveolar concentrations of desflurane or sevoflurane compared with isoflurane in normoventilated pigs. *J Neurosurg Anesthesiol* 2003; **15**: 90–7.
6. Mapleson WW. Effect of age on MAC in humans: a meta-analysis. *Br J Anaesth* 1996; **76**: 179–85.
7. Thornton C. Evoked potentials in anaesthesia. *Eur J Anaesthesiol* 1991; **8**: 89–107.
8. Kalkman CJ, Drummond JC. Monitors of depth of anesthesia, quo vadis? *Anesthesiology* 2002; **96**: 784–7.
9. Alpiger S, Helbo-Hansen HS, Jensen EW. Effect of sevoflurane on the mid-latency auditory evoked potentials measured by a

new fast extracting monitor. *Acta Anaesthesiol Scand* 2002; **46**: 252–6.
10. Litvan H, Jensen EW, Revuelta M, Henneberg SW et al. Comparison of auditory evoked potentials and the A-line ARX Index for monitoring the hypnotic level during sevoflurane and propofol induction. *Acta Anaesthesiol Scand* 2002; **46**: 245–51.
11. Gosling RG, King DH. Arterial assessment by Doppler shift ultrasound. *Proc R Soc Med* 1974; **67**: 447–9.
12. Paul M, Fisher DM. Are estimates of MAC reliable? *Anesthesiology* 2001; **95**: 1362–70.
13. Lu W, Ramsay JG, Bailey JM. Reliability of pharmacodynamic analysis by logistic regression: Mixed effects modeling. *Anesthesiology* 2003; **99**: 1255–62.
14. Rampil IJ. Anesthetic potency is not altered after hypothermic spinal cord transection in rats. *Anesthesiology* 1994; **80**: 606–10.
15. Jensen EW, Nebot A, Caminal P, Henneberg SW. Identification of causal relations between haemodynamic variables, auditory evoked potentials and isoflurane by means of fuzzy logic. *Br J Anaesth* 1999; **82**: 25–32.
16. Kurita T, Doi M, Katoh T, Sano H et al. Auditory evoked potential index predicts the depth of sedation and movement in response to skin incision during sevoflurane anesthesia. *Anesthesiology* 2001; **95**: 364–70.
17. Struys MM, Vereecke H, Moerman A et al. Ability of the bispectral index, autoregressive modeling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil. *Anesthesiology* 2003; **99**: 802–12.
18. Bishop CC, Powell S, Rutt D, Browse NL. Transcranial Doppler measurements of middle cerebral artery blood flow velocity: a validation study. *Stroke* 1986; **17**: 913–5.
19. Mühling J, Dehne MG, Sablotzki A, Mühling A, Hempelmann G. Effects of theofylline on human cerebral blood flow velocity during halothane and isoflurane anaesthesia. *Eur J Anaesth* 1999; **16**: 380–6.
20. Ebert TJ, Robinson BJ, Uhrich TD, Mackenthun A et al. Recovery from sevoflurane anesthesia: a comparison to isoflurane and propofol anesthesia. *Anesthesiology* 1998; **89**: 1524–31.
21. Summors AC, Gupta AK, Matta BF. Dynamic cerebral autoregulation during sevoflurane anesthesia: a comparison with isoflurane. *Anesth Analg* 1999; **88**: 341–5.
22. Hisada K, Morioka T, Fukui K, Nishio S et al. Effects of sevoflurane and isoflurane on electrocorticographic activities in patients with temporal lobe epilepsy. *J Neurosurg Anesthesiol* 2001; **13**: 333–7.
23. Artru AA, Lam AM, Johnson JO, Sperry RJ. ICP, middle cerebral artery flow velocity, and plasma inorganic fluoride concentrations in neurosurgical patients receiving sevoflurane or isoflurane. *Anesth Analg* 1997; **85**: 587–92.
24. Zbornikova V, Lassvik C, Hillman J. Intracranial haemodynamics during vasomotor stress test in unilateral carotid artery occlusion estimated by 3-D transcranial Doppler scanner. *Neurol Res* 1995; **17**: 137–43.

Address:
Anders Holmström, MD, DEAA, EDIC
Department of Anesthesia and Intensive Care
Malmö University Hospital 04226
SE-205 02 Malmö
Sweden
e-mail: anders.holmstrom@skane.se