Anesthesiology
2000; 92:55–61

Influence of Age on Hypnotic Requirement, Bispectral Index, and 95% Spectral Edge Frequency Associated with Sedation Induced by Sevoflurane

Takasumi Katoh, M.D., Hiromichi Bito, M.D.,* Shigehito Sato, M.D.†*

Background: **Aging is associated with a reduction in anesthetic requirements. The effects of age on the electroencephalographic response to inhalational anesthesia have not been well documented. The objective of the present study was to determine the influence of age on hypnotic requirement and electroencephalographic derivatives such as bispectral index and 95% spectral edge frequency associated with sedation induced by sevoflurane.**

Methods: **Ninety-six patients were randomly allocated into one of three age groups A, B, and C, ranging in age from 18–39 yr, 40–64 yr, and 65–85 yr, respectively. Patients in each group were sedated with sevoflurane at two predetermined concentrations ranging between 0.45% and 0.85%. The relationship between sevoflurane concentration and response to a verbal command, as well as the relationships between response and bispectral index and 95% spectral edge frequency, was determined.**

Results: **Multiple regression analysis showed that end-tidal sevoflurane concentration and age significantly affected both bispectral index and 95% spectral edge frequency. ED_{50} values of sevoflurane concentration for loss of consciousness, defined as no response to verbal command, were different between groups A and C: 0.72 (95% confidence interval: 0.68–0.75) *versus* 0.59 (95% confidence interval: 0.56–0.62). However, the same effective values of bispectral index and 95% spectral edge frequency at this same clinical end point did not differ.**

Conclusions: **Increasing age reduced sevoflurane requirements to suppress responses to a verbal command but did not change bispectral index and 95% spectral edge frequency associated with this end point, and in a population with a wide age range, bispectral index would predict depth of sedation better than end-tidal sevoflurane concentration. (Key words: Anesthetic potency; gender; prediction probability.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

* Assistant Professor.

† Professor and Chairman.

Received from the Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, Hamamatsu, Japan. Submitted for publication April 8, 1999. Accepted for publication July 27, 1999. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Katoh: Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, 431-3192 Japan. Address electronic mail to: tackatoh@hama-med.ac.jp

AGE is one of the many factors known to influence the minimum alveolar concentration (MAC) that prevents movement in response to a noxious stimulus in 50% of a population, or that suppresses response to a verbal command (MAC_{awake}).[1–4] An inverse relationship between age and anesthetic or hypnotic requirement is reported for sevoflurane and isoflurane.[4,5] The electroencephalogram (EEG) is known to change with the depth of sedation and general anesthesia level. Recent studies demonstrated that real-time processed EEG data, such as bispectral index (BIS) or 95% spectral edge frequency (95% SEF), correlate well with hypnotic and sedative end points such as sedation level, loss of consciousness, lack of awareness, and memory.[6,7] The BIS and 95% SEF values at which 50% of patients are adequately sedated have been determined in many studies, and this information is clinically valuable. Although BIS is reported to be independent of the anesthetics used,[7] the influence of patient age on BIS or 95% SEF has not been well documented.

The objective of the present study was to determine the influence of age on hypnotic requirement, BIS, and 95% SEF associated with sedation induced by sevoflurane.

Material and Methods

After approval for this study had been obtained from the ethics committee of Hamamatsu University Hospital, informed consent to participate was acquired from all patients. The study group included 96 patients having American Society of Anesthesiologists physical status of I or II who were scheduled for elective surgery. Exclusion criteria were a history of cardiac, pulmonary, or

renal disease; a history of esophageal reflux or hiatal hernia; drug or alcohol abuse; significant obesity (body mass index > 30); and contraindication for an inhalational induction.

Patients were assigned to one of three age groups, each having 32 subjects. Groups A, B, and C ranged in age from 18–39 yr, 40–64 yr, and 65–85 yr, respectively. Patients fasted for at least 8 h before surgery and received no premedicant drugs.

Electroencephalographic electrodes (Zipprep, Aspect Medical Systems, Natick, MA) were placed in the following configuration: bipolar frontomastoid montage (Fp1-A1 and Fp2-A2 in the International 10-20 System of electrode placement). The impedance of each electrode was less than 2 kΩ. EEG parameters including BIS (software version 3.2) and 95% SEF were recorded continuously using an Aspect A1,000 EEG monitor. Data were averaged online from the combined two leads because similar results were obtained from two channels. The BIS and 95% SEF values were calculated by averaging the values recorded for these variables during the 45-s interval immediately before assessment. To minimize artifacts, patients were instructed not to open their eyes, talk, or move during the EEG recording. Four artifact-detection schemes (slew rate, suppression, motion, and high frequency) were enabled. If these artifacts were detected, EEG parameters were excluded from contributing to the mean BIS or SEF. Serial output files consisting of processed EEG parameters were collected on a personal computer.

All patients breathed through a face mask connected to a semiclosed anesthetic circuit. To prevent contamination of end-tidal samples with inspired gas, the dead space was augmented at the sampling port using an extension tube. Gas was drawn continuously from the sampling port, which was located between the face mask and the dead space. The concentrations of carbon dioxide, sevoflurane, and oxygen were measured continuously by means of an infrared anesthetic gas analyzer (Capnomac, Datex, Helsinki, Finland), which was calibrated using a standard gas mixture before anesthesia for each patient. These concentrations were recorded every 10 s throughout the study period simultaneously with EEG parameters using a desktop computer (Macintosh Classic, Apple Computer, Tokyo, Japan).

Patients were sedated with sevoflurane and oxygen first during spontaneous ventilation, then during assisted ventilation if required, to keep the tidal volume high enough to measure the end-tidal anesthetic concentrations. End-tidal carbon dioxide concentration was kept between 35 and 45 mmHg during the study period. Inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration constant at a value set according to predetermined randomization scheme. After maintaining this target concentration for 15 min to allow blood:brain equilibration of sevoflurane, depth of sedation was assessed using the responsiveness component of the Observer's Assessment of Alertness/Sedation (OAA/S) rating scale (table 1).[8] This assessment procedure involves presentation of progressively more intense stimulation, ranging from a moderate speaking voice to physical shaking or moderate noxious stimuli (trapezius squeeze), until a response is observed. These stimuli were applied at 15-s intervals. The EEG parameters were recorded just before assessing sedation level. To calculate ED_{50} values of sevoflurane concentration, BIS, and 95% SEF for loss of consciousness, we judged patients to be conscious if the OAA/S score was between 3 and 5 and unconscious if the OAA/S score was < 3. This assessment was performed twice per patient at different sevoflurane concentrations. The first concentration was selected randomly from among 0.50, 0.55, 0.60, and 0.65% for groups A and B and from among 0.45, 0.50, 0.55, and 0.60% for group C, and the second concentration was 0.2% higher than the first concentration.

Table 1. Responsiveness Scores of the Modified Observer's Assessment of Alertness/Sedation Scale

Responsiveness	Score
Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

To minimize interobserver variability, one investigator (T. K.) blinded to sevoflurane concentrations and EEG parameters performed all assessments.

Statistical Analysis

Multiple linear regression, using a statistical software package (Statview II, Abacus Concept, Berkeley, CA), determined if end-tidal sevoflurane concentration, age, or gender affected BIS or 95% SEF.

The performance of hypnotic depth indicators such as sevoflurane concentration, BIS, and 95% SEF to predict depth of sedation was evaluated using prediction prob-

Table 2. Demographic Data

	Group A	Group B	Group C
Number	32	32	32
Age (yr)			
Mean ± SD	28 ± 7	51 ± 6	70 ± 5
Range	18–39	40–63	65–82
Gender			
Male	17	14	16
Female	15	18	16
Body weight (kg) ± SD	54 ± 12	56 ± 11	50 ± 12

ability (Pk), which compares the performance of indicators having different units of measurement. The mathematical basis of Pk was described by Smith *et al.*[9] A Pk value of 1 means that the predicting variable (*e.g.*, hypnotic depth indicator) always correctly predicts the value of the variable to be predicted (*e.g.*, true observed depth of sedation). A value of 0.5 means that the values of the indicator predict no better than a 50:50 chance (like flipping a fair coin). A value of Pk was computed for each group, and also for combined groups. The jackknife method was used to compute the standard error of the estimate, based on the assumption that the verbal commands were independent. A paired-data jackknife analysis was used to determine whether the Pk value of sevoflurane concentration differed from those of the EEG parameters within a group. To compare the performance of an indicator among the groups, a *t* test was performed using the jackknife results. For multiple comparisons, we applied the Bonferroni correction. Calculation of Pk was performed by using a custom spreadsheet macro.

We estimated ED_{50} values of sevoflurane concentration, BIS, and 95% SEF for loss of consciousness using a logistic regression analysis described by Waud.[10] The ED_{50} values for the three age groups were compared by Waud's technique. $P < 0.05$ was considered significant.

Results

Characteristics of the 96 patients participating in this study are presented in table 2. Multiple regression analysis showed that end-tidal sevoflurane concentration and age significantly affected both BIS and 95% SEF. Both BIS and 95% SEF decreased in a dose-dependent manner with increasing end-tidal sevoflurane concentration (figs. 1 and 2).

Pk values for predicting depth of sedation are presented in table 3. In any age group, all indicators predicted depth of sedation significantly better than a 50:50 chance. No significant difference in Pk was observed between sevoflurane concentration and BIS, and Pks for BIS and sevoflurane concentration differed significantly from those for 95% SEF ($P < 0.05$). In the combined group, the Pk values (based on all 192 assessments) were 0.883 ± 0.013 (SE) for sevoflurane concentration, 0.926 ± 0.010 for BIS, and 0.831 ± 0.017 for 95% SEF. Pks for BIS and sevoflurane concentration differed significantly from those for 95% SEF, and Pk for BIS was different from that for sevoflurane concentration ($P < 0.05$). There were no differences in Pk of any indicator between groups.

The relationships between sevoflurane concentration,

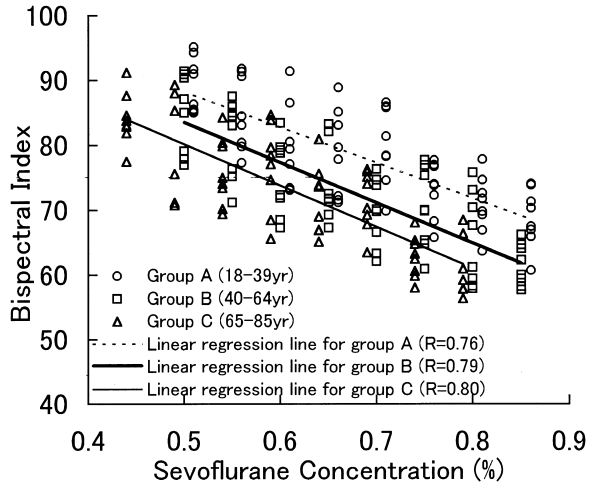

Fig. 1. Scatter diagram showing the relation between bispectral index and end-tidal sevoflurane concentration in various age groups.

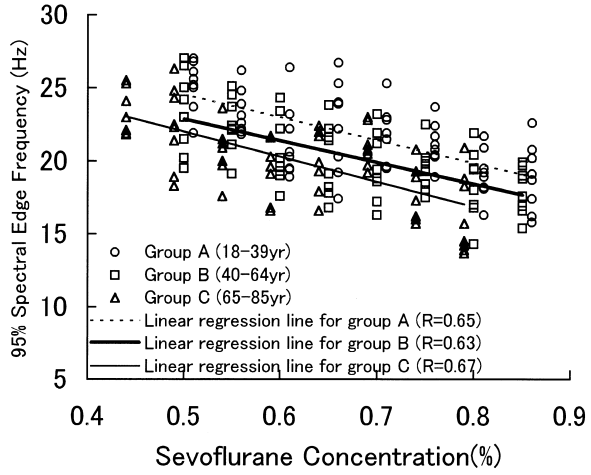

Fig. 2. Scatter diagram showing the relation between 95% spectral edge frequency and end-tidal sevoflurane concentration in various age groups.

Table 3. Prediction Probability (Pk ± SE) of Sevoflurane Concentration, Bispectral Index, and 95% Spectral Edge Frequency for Three Age Groups and Combined Group

Group	No. of Observation	Sevoflurane Concentration (%)	BIS	95% SEF
A (18–39 yr)	64	0.914 ± 0.013	0.929 ± 0.019	0.840 ± 0.027*†
B (40–64 yr)	64	0.908 ± 0.019	0.964 ± 0.011	0.809 ± 0.034*†
C (65–85 yr)	64	0.919 ± 0.018	0.907 ± 0.018	0.854 ± 0.032*†
Combined	192	0.883 ± 0.013	0.926 ± 0.010*	0.831 ± 0.017*†

Data are mean ± SD, where appropriate.

BIS = bispectral index; SEF = spectral edge frequency.

* $P < 0.05$ *vs.* sevoflurane concentration.

† $P < 0.05$ *vs.* BIS.

BIS, and 95% SEF and the probability of loss of consciousness for the three age groups are presented in figures 3–5. ED_{50} values of sevoflurane (equivalent to MAC_{awake}), BIS, and 95% SEF for the three groups and the combined group are listed table 4. There was a significant difference in the ED_{50} value of sevoflurane between group A and B; no difference was observed in the ED_{50} values of BIS and 95% SEF.

Discussion

The EEG patterns are known to change in relation to the depth of sedation[7] and level of general anesthesia.[11,12] In the present study, BIS was related linearly to sevoflurane concentration over the entire study range in all age groups. This finding is consistent with previous studies on sevoflurane and isoflurane.[6,7] BIS seemed to decreased linearly with increasing anesthetic concentrations in a sedative range, with inhalational as well as intravenous anesthetics.[7,13] 95% SEF was also related linearly to sevoflurane concentration over the entire study range in all age groups. Previous studies demonstrated that quantitative EEG parameters such as 95% SEF varied predictably with increasing end-tidal sevoflurane concentrations, and that the EEG response to increasing sevoflurane was biphasic: An initial increase of EEG parameters from the awake state was followed by EEG slowing and a decrease in the EEG parameters.[6,14] In the present study, we did not include EEG data obtained at

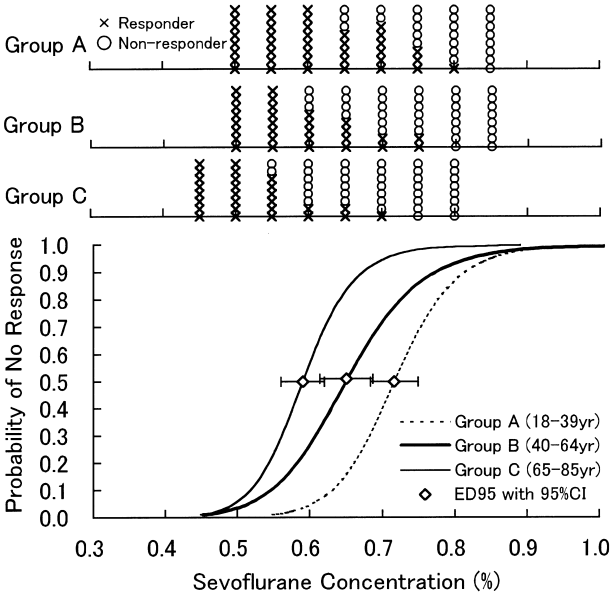

Fig. 3. Probability of no response to loud verbal command as a function of the end-tidal sevoflurane concentration. In the upper part of the figure, individual observations are presented. In the lower part, the values are ED_{50}s with 95% confidence intervals.

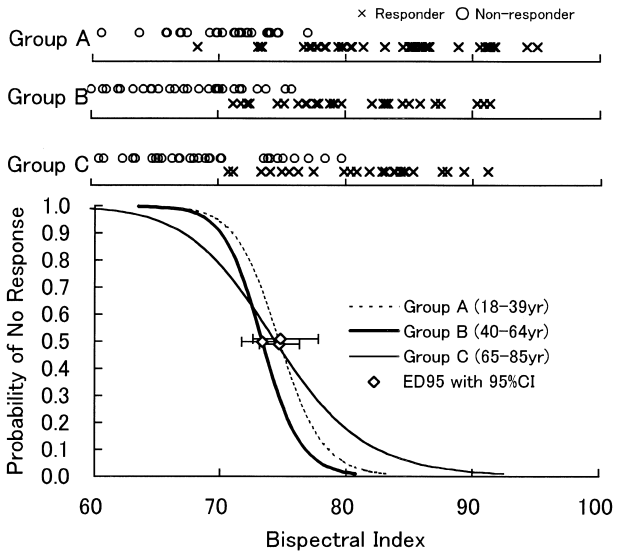

Fig. 4. Probability of no response to loud verbal command as a function of the bispectral index. In the upper part of the figure, individual observations are presented. In the lower part, the values are ED_{50}s with 95% confidence intervals.

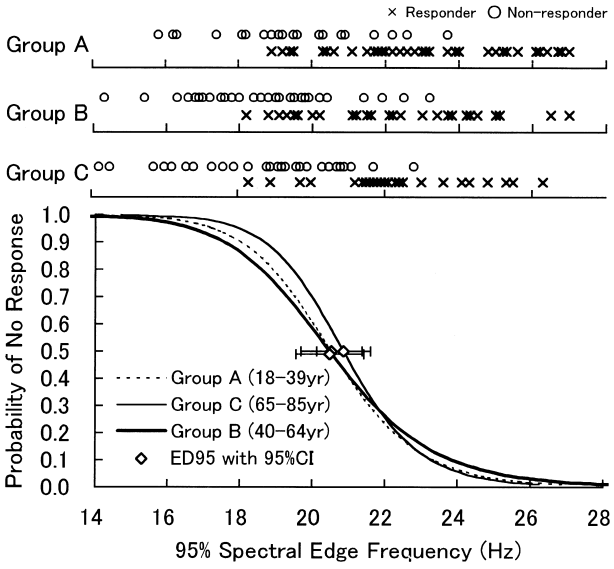

Fig. 5. Probability of no response to loud verbal command as a function of the 95% spectral edge frequency. In the upper part of the figure, individual observations are presented. In the lower part, the values are ED_{50}s with 95% confidence intervals.

end-tidal concentrations less than 0.4%, at which the EEG parameter would initially increase with increasing sevoflurane concentrations. Our findings on the linear relationship between sevoflurane concentration and EEG parameters agree with those of these previous studies.

Altered sensitivity to anesthetics in elderly patients has been widely reported for both inhalational and intravenous anesthesia.[2,3,15–20] For intravenous anesthetics, these changes in drug action are caused by age-related alterations in drug disposition, end-organ sensitivity, or a combination of both. Age-related changes in drug disposition of intravenous anesthetics have been shown in many studies.[16,17,20,21] There were no age-related changes in brain responsiveness or pharmacodynamics if the EEG parameter is used as a measure of thiopental effect.[16,17] In contrast, increasing pharmacodynamic sensitivity to propofol in elderly patients was reported.[22] The effect of age on pharmacodynamics may be dependent on the intravenous drug used and may be different between intravenous and inhalational anesthetics.

The importance of age on the EEG response to anesthesia has not been well documented for inhalational anesthetics. EEG changes in patients in response to different concentrations of isoflurane or halothane have been described, but the relationship of age to these responses has not been evaluated.[23–25] We found that age was a significant independent variable in the analysis of BIS and 95% SEF during sedation induced by sevoflurane. A previous study showed that the proportion of time in EEG burst suppression was significantly greater in elderly patients than that observed in younger controls at 1.7% end-tidal isoflurane concentration, and that the frequency of EEG burst-suppression events was greater in elderly subjects.[26] This demonstrates a discrete alteration relative to age in the central nervous system sensitivity to isoflurane. Another study showed that isoflurane and desflurane produced a similar increase in EEG burst suppression with increasing anesthetic concentration in neurosurgical patients, and that the EEG burst suppression was affected by the age of the patient. This is consistent with our findings, although the anesthetic concentrations used in the previous studies were much higher than those used in this one. Although it is clear that age affects MAC requirements during inhalational anesthesia,[1–3] the relationship between EEG and MAC is inconclusive. EEG derivatives do not necessarily predict depth of anesthesia as defined by the response to surgical incision.[6,23] This may be because of independent sites of action of anesthetics on EEG and MAC within the central nervous system.[27–29] An increased brain sensitivity (as determined by EEG changes) in the elderly has been reported in association with fentanyl, alfentanil, and remifentanil.[15,20] In contrast, other studies have demonstrated that age has no effect on the alfentanil plasma concentration required for suppressing responses to noxious stimuli.[18,30,31] It is possible that changes in potency reflected in the EEG may not reflect changes in potency for some clinical end points.

The influence of aging on pharmacokinetics is an important factor in determining anesthetic requirements. We maintained target concentrations for 15 min to allow blood:brain equilibration of sevoflurane, which is probably long enough,[32,33] although the influence of aging on blood:brain equilibration of sevoflurane has been unknown. BIS values were indeed stable a few minutes before depth of sedation was assessed.

Our previous study demonstrated MAC_{awake} decreases at a rate similar to the rate of decreases in MAC relative to increasing age; therefore, the ratios to MAC can be considered fairly constant and are 0.34 for both sevoflurane and isoflurane.[4] Although our finding of a decrease in MAC_{awake} in the elderly is consistent with that in the previous study, the rate of decrease in MAC_{awake} relative to increasing age seems smaller. In other words, the decrease in MAC_{awake} obtained in the elderly in the present study may be greater than that predicted with the regression line obtained in the previous study. However, the prediction of MAC_{awake} for patients older than

Table 4. ED_{50} Values (95% Confidence Interval) of Sevoflurane Concentration, Bispectral Index, and 95% Spectral Edge Frequency for Loss of Consciousness in Three Age Groups and Combined Group

Group	No. of Observation	Sevoflurane Concentration (%)	BIS	95% SEF
A (18–39 yr)	64	0.72 (0.68–0.75)	74.7 (73.1–76.3)	20.5 (19.7–21.4)
B (40–64 yr)	64	0.65 (0.62–0.69)	73.4 (71.6–75.0)	20.5 (19.6–21.4)
C (65–85 yr)	64	0.59 (0.56–0.62)*	74.8 (72.5–77.2)	20.9 (20.1–21.6)
Combined	192	0.65 (0.63–0.67)	74.3 (73.2–75.4)	20.6 (20.1–22.1)

BIS = bispectral index; SEF = spectral edge frequency.

* $P < 0.05$ *vs.* group A.

65 yr may be overextended, given that the previous study did not include such patients. Several explanations for the discrepancy are possible. In the previous study, MAC_{awake} was measured after surgery and the laryngeal mask airway was used, but in the present study MAC_{awake} was measured before surgery and an anesthesia face mask was used. MAC_{awake} measured after surgery may be affected by the severity of postoperative pain. Severe postoperative pain would be a stronger stimuli with greater potential to awaken patients, resulting in a higher MAC_{awake} value. Relative to advancing age, the decrease in MAC_{awake} obtained postoperatively would be greater than that in MAC_{awake} free from postoperative pain, because pain thresholds in both somatic and visceral stimuli increase with advancing age.[34,35] The influence of postoperative pain on MAC_{awake} might be different between younger and elderly patients in the previous study.

Some observations suggest that motor responses to a noxious stimulus may be primarily mediated by subcortical structures including the spinal cord, at least in lower animals.[27–29] In contrast, purposeful responsiveness to a verbal command apparently presupposes intact cortex function. These observations reveal that different sites of action determine MAC and MAC_{awake}. Therefore, a drug does not necessarily produce the same effect on both MAC and MAC_{awake}; *i.e.*, fentanyl reduced sevoflurane requirements for both loss of consciousness and surgical incision, but the reduction modes were not comparable at the two end points,[36] and a single parameter that can predict responses at one end point does not necessarily predict responses at the other end point.[6] Similarly, it is possible that the effect of the physiologic status of the patient, including variables such as age, does not produce the same change in both MAC and MAC_{awake}.

The finding that aging reduced MAC more than MAC_{awake} suggests that, if physicians adjusted sevoflurane concentration using the movement/no movement end point (MAC end point) to provide adequate anesthesia, elderly patients would be awake (MAC_{awake} end point) earlier on emergency from anesthesia than younger patients. However, this may not be the case with clinical anesthesia, because the end points used in anesthetizing surgical patients are usually hemodynamic parameters such as arterial blood pressure and heart rate, and the influence of age on MAC and blocking adrenergic responses remains unclear.

In contrast to the dependence of MAC_{awake} on age with regard to application of sevoflurane, both BIS and 95% SEF values at which responses to loud verbal commands were suppressed in 50% of patients were not affected by the age of the patient. The influence of age on the efficacy of the EEG parameter to assess depth of sedation or anesthesia has not been well documented. We found no difference in Pk between the combined group and any age group. However, the Pk value for sevoflurane in predicting the depth of sedation did not differ from that for BIS in any age group, though the Pk value for sevoflurane significantly differed from that for BIS in the combined group. Further, MAC_{awake} value was significantly affected by age. We calculated Pk of the EEG parameters for predicting depth of sedation expressed on an OAA/S rating scale having six levels, not only for predicting the MAC_{awake} end point. This means the EEG parameters are independent of age in predicting depth of sedation ranging from deep to light.

In conclusion, we found that (1) aging significantly affected the reduction in BIS and 95% SEF induced by sevoflurane; (2) during sevoflurane, aging reduced MAC_{awake} but did not change BIS and 95% SEF associated with response to a verbal command; and (3) in a population with a wide age range, BIS would predict depth of sedation better than end-tidal sevoflurane concentration.

The authors thank the staff at Hamamatsu University Hospital for their support of this work, and Dr. Shibutani at New York Medical College for his encouragement and numerous suggestions.

References

1. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI, Miller RD, de Jong RH, Elashoff RM: Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. ANESTHESIOLOGY 1975; 42:197–200

2. Gold MI, Abello D, Herrington C: Minimum alveolar concentration of desflurane in patients older than 65 yr. ANESTHESIOLOGY 1993; 79:710–4

3. Nakajima R, Nakajima Y, Ikeda K: Minimum alveolar concentration of sevoflurane in elderly patients. Br J Anaesth 1993; 70:273–5

4. Katoh T, Suguro Y, Ikeda T, Kazama T, Ikeda K: Influence of age on awakening concentrations of sevoflurane and isoflurane. Anesth Analg 1993; 76:348–52

5. Katoh T, Ikeda K: Minimum alveolar concentration of sevoflurane in children. Br J Anaesth 1992; 68:139–41

6. Katoh T, Suzuki A, Ikeda K: Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. ANESTHESIOLOGY 1998; 88:642–650

7. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. ANESTHESIOLOGY 1997; 86:836–47

8. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51

9. Smith WD, Dutton RC, Smith NT: Measuring the performance of anesthetic depth indicators. ANESTHESIOLOGY 1996; 84:38–51

10. Waud DR: On biological assays involving quantal responses. J Pharmacol Exp Ther 1972; 183:577–607

11. Thomsen CE, Christensen KN, Rosenfalck A: Computerized monitoring of depth of anaesthesia with isoflurane. Br J Anaesth 1989; 63:36–43

12. Vernon JM, Lang E, Sebel PS, Manberg P: Prediction of movement using bispectral electroencephalographic analysis during propofol/alfentanil or isoflurane/alfentanil anesthesia. Anesth Analg 1995; 80:780–5

13. Doi M, Gajraj RJ, Mantzaridis H, Kenny GN: Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia: Comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index. Br J Anaesth 1997; 78:180–4

14. Tatsumi K, Hirai K, Furuya H, Okuda T: Effects of sevoflurane on the middle latency auditory evoked response and the electroencephalographic power spectrum. Anesth Analg 1995; 80:940–3

15. Scott JC, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age: A simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 1987; 240:159–66

16. Stanski DR, Maitre PO: Population pharmacokinetics and pharmacodynamics of thiopental: The effect of age revisited. ANESTHESIOLOGY 1990; 72:412–22

17. Homer TD, Stanski DR: The effect of increasing age on thiopental disposition and anesthetic requirement. ANESTHESIOLOGY 1985; 62: 714–724

18. Lemmens HJ, Bovill JG, Hennis PJ, Burm AG: Age has no effect on the pharmacodynamics of alfentanil. Anesth Analg 1988; 67:956–60

19. Lemmens HJ, Burm AG, Hennis PJ, Gladines MP, Bovill JG: Influence of age on the pharmacokinetics of alfentanil: Gender dependence. Clin Pharmacokinet 1990; 19:416–22

20. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil: I. Model development. ANESTHESIOLOGY 1997; 86:10–23

21. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. ANESTHESIOLOGY 1998; 88:1170–82

22. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. ANESTHESIOLOGY 1999; 90:1502–16

23. Dwyer RC, Rampil IJ, Eger En, Bennett HL: The electroencephalogram does not predict depth of isoflurane anesthesia. ANESTHESIOLOGY 1994; 81:403–9

24. Yli-Hankala A, Eskola H, Kaukinen S: EEG spectral power during halothane anaesthesia: A comparison of spectral bands in the monitoring of anaesthesia level. Acta Anaesthesiol Scand 1989; 33:304–8

25. Schwilden H, Stoeckel H: Quantitative EEG analysis during anaesthesia with isoflurane in nitrous oxide at 1.3 and 1.5 MAC. Br J Anaesth 1987; 59:738–45

26. Schwartz AE, Tuttle RH, Poppers PJ: Electroencephalographic burst suppression in elderly and young patients anesthetized with isoflurane. Anesth Analg 1989; 68:9–12

27. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain. ANESTHESIOLOGY 1993; 79:1244–9

28. Rampil IJ: Anesthetic potency is not altered after hypothermic spinal cord transection in rats. ANESTHESIOLOGY 1994; 80:606–10

29. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. ANESTHESIOLOGY 1993; 78:707–12

30. Lemmens HJ, Burm AG, Bovill JG, Hennis PJ: Pharmacodynamics of alfentanil as a supplement to nitrous oxide anaesthesia in the elderly patient. Br J Anaesth 1988; 61:173–9

31. Ausems ME, Hug CC, Jr, Stanski DR, Burm AG: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. ANESTHESIOLOGY 1986; 65:362–73

32. Katoh T, Suguro Y, Kimura T, Ikeda K: Cerebral awakening concentration of sevoflurane and isoflurane predicted during slow and fast alveolar washout. Anesth Analg 1993; 77:1012–7

33. Olofsen E, Dahan A: The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. ANESTHESIOLOGY 1999; 90:1345–53

34. Kasamatsu T, Miyashita K, Shiomi S, Iwata H: The effect of aging on the peripheral functions in farmers and chain saw operators, part 1: Age-related changes in pain and vibratory sense thresholds. Sangyo Igaku 1981; 23:127–33

35. Lasch H, Castell DO, Castell JA: Evidence for diminished visceral pain with aging: Studies using graded intraesophageal balloon distension. Am J Physiol 1997; 272:G1–3

36. Katoh T, Ikeda K: The effects of fentanyl on sevoflurane requirements for loss of consciousness and skin incision. ANESTHESIOLOGY 1998; 88:18–24