Interaction of Propofol and Sevoflurane on Loss of Consciousness and Movement to Skin Incision during General Anesthesia

Robert S. Harris, M.D., *Olga Lazar, M.D.,* *Jay W. Johansen, M.D, Ph.D.,†* *Peter S. Sebel, M.B.B.S., Ph.D., M.B.A.‡*

Background: Loss of consciousness (LOC) and immobility to surgical incision seem to be mediated at different levels of the central nervous system. Pharmacologic studies of hypnotic agents have previously focused on combinations of either volatile or intravenous anesthetics. This study examined the combination of inhaled sevoflurane and intravenous propofol at these two clinically relevant anesthetic end points.

Methods: Thirty-six elective surgical patients were initially enrolled. Conditions approximating steady state were obtained for sevoflurane and target-controlled propofol infusions. Patients were sequentially evaluated for LOC (loud voice plus mild prodding) and immobility to surgical incision. The study was designed using the Dixon up–down method.

Results: The observed propofol effect target with 50% response plus sevoflurane (0.46% end-tidal concentration) was 1.2 μg/ml (95% confidence interval, 1.1–1.3 μg/ml). It was not significantly different from that predicted (1.5 μg/ml; 95% confidence interval, 1.2–1.7 μg/ml) by simple additivity. The effective plasma concentration of propofol that suppressed movement to skin incision in 50% of patients was 5.4 μg/ml (95% confidence interval, 4.8–6.0 μg/ml) plus sevoflurane (0.86%) and was not significantly different from that predicted by additivity (5.4 μg/ml; 95% confidence interval, 4.8–5.9 μg/ml). Both analyses had adequate power (90%) to detect a significant change (±19 to 25%) from predicted value. Repeated-measures analysis of variance identified a Bispectral Index value of 70 as the break point between those who responded at LOC or did not.

Conclusions: Propofol and sevoflurane interact in a simple additive manner to produce LOC and immobility to surgical incision, suggesting a common mechanism or a single site of action. These clinical observations are consistent with a single site of interaction at the γ-aminobutyric acid type A receptor.

ANESTHETIC requirement for surgery has historically been defined in terms of the minimum alveolar concentration of a volatile anesthetic (MAC) that will suppress movement to skin incision in 50% of patients.[1] The movement response to skin incision (nociception) has been shown to be medi-

---

This article is accompanied by an Editorial View. Please see: Hemmings HC Jr: Do general anesthetics add up? ANESTHESIOLOGY 2006; 104:1120–2.

---

ated at the spinal cord level and is not necessarily related to hypnosis or amnesia mediated at higher cortical centers in the brain.[2–4] It has been proposed that different neuronal systems mediate the diverse actions of general anesthetics and that specific neurotransmitter-receptor subtypes can be linked to defined parts of the pharmacologic spectrum of these drugs.[5,6] Because the loss of consciousness (LOC) and the immobility response to surgical incision (measured by MAC) seem to be mediated at different levels in the central nervous system, this clinical study investigated the interaction between propofol and sevoflurane for both LOC and MAC.

The dose requirements for propofol or sevoflurane used alone have been well validated in human subjects. Sevoflurane MAC is 1.71%.[7,8] The effective plasma concentration of propofol that will suppress movement to skin incision in 50% of patients (Cp_{50INC}) is 15.2 μg/ml.[9] The end-tidal concentration of sevoflurane that will produce LOC in 50% of patients (LOC_{50sevo}) is 0.89%, and the equivalent effect site concentration of propofol for loss of consciousness (Cp_{50LOC}) is 2.81 μg/ml.[10]

The lack of a defined molecular target and selective antagonists has limited previous pharmacologic investigations of hypnotic/anesthetic mechanisms to interactions between two volatile anesthetics[11–15] or between intravenous agents.[16–21] Eger *et al.*[11] combined halothane and isoflurane and determined that the effects of the 2 agents on MAC were additive. The interaction of volatile and intravenous anesthetics has been studied in rats.[22] Thiopental was shown to reduce halothane requirements in a log-linear manner (not simple additivity). Drug interaction studies on sedation have focused on midazolam–propofol interactions.[17,20,23]

Propofol, etomidate, and midazolam have been proposed to produce sedation and immobilization through interaction with the γ-aminobutyric acid type A receptor.[5,24,25] Although volatile anesthetics are thought to produce immobilization through a different mechanism,[26,27] some *in vivo* evidence suggests that the γ-aminobutyric acid type A receptor may also play a role in humans.[28] Because the sites of action of anesthetics in producing LOC and immobility seem to be different and various putative sites of anesthetic agents have been identified, defining the volatile/intravenous anesthetic interaction for these agents at two clinically relevant end points may provide another tool to help further define the mechanism of action of anesthesia. A companion article describes the interaction of the same two agents at the γ-aminobutyric acid type A receptor *in vitro*.[29]

1170

Materials and Methods

After Institutional Review Board (Emory University, Atlanta, Georgia) approval and written informed consent were obtained, patients with American Society of Anesthesiologists physical status of I or II, aged 18–55 yr, presenting for elective surgery, and requiring a skin incision of more than 1 inch were enrolled. Ineligibility criteria included serious hearing impairment (inability to comprehend speech at normal tone of voice), chronic substance abuse, weight greater than 150% of ideal body weight, and neurologic or seizure disorders. Patients who were not fluent in English or had used opioids within 8 h before surgery were also excluded.

Patients were recruited during preoperative preparation before surgery. No preoperative sedation or analgesics were administered. In the operating room, standard anesthesia monitors were placed, including an electrocardiograph, pulse oximeter, noninvasive blood pressure, Bispectral Index of the electroencephalogram (BIS), and end-tidal gas (ET_{sevo} and $ETco_2$) monitors. The Bispectral Index A2000 monitor® (version 3.3; Aspect Medical Systems, Inc., Natick, MA) uses three adhesive electrodes to the forehead (single channel: Fp1–Fpz). BIS, raw electroencephalogram, electromyogram (70- to 110-Hz band referenced to 100 μV in decibels), electrode impedance (ohms), and signal quality index (a global estimate of data quality from 0 to 100) were automatically recorded to a computer at 5-s intervals. BIS and other electroencephalographic variables are an average of recordings taken for 1 min before administration of sedation scale or MAC determination. Hemodynamic variables and end-tidal gas measurements were recorded manually. No other intraoperative medications were administered during the study.

Loss of Consciousness

Sevoflurane (tightly sealed mask *via* semiclosed circuit) was administered to achieve an end-tidal concentration of 0.45% (half LOC_{50sevo}).[10] Propofol target-controlled infusion used STANPUMP,§ programmed with the pharmacokinetic parameters of Schnider,[30] and a Harvard syringe pump (South Natick, MA) to a preset "effect site" concentration. The initial propofol target (effect site) concentration used was 1.4 μg/ml.[10] After 10 min of equilibration at the target concentration (approximately 3 distribution time constants), the modified Observer's Assessment of Alertness/Sedation (OAA/S)[31] was administered. LOC was defined as an OAA/S score less than 2 (loss of responsiveness to voice command [open eyes] with light tapping on the shoulder or mild shaking). This arousal response or opening the eyes was

considered positive, whereas nonspecific (nonpurposeful) motor responses were considered negative.

Movement Response

After administration of the OAA/S, the concentration of sevoflurane was increased to 0.85% (half MAC_{sevo}),[8] and the propofol target-controlled infusion effect site target was increased to 7.6 μg/ml (half Cp_{50INC}).[9] The patient's trachea was intubated after administration of succinylcholine (1.5 mg/kg). The lungs were ventilated to maintain an end-tidal carbon dioxide concentration between 32 and 35 mmHg. After at least a 10-min equilibration at the target end-tidal anesthetic concentration and return of neuromuscular function (train-of-four), skin incision was performed. Movement was defined as gross movement of limbs, head, or body. Coughing, chewing, and swallowing were not considered movement.

Dixon Method

The target concentrations of sevoflurane for OAA/S and for incision were not altered during the study. However, the propofol target-controlled infusion targets used for each subsequent patient (Cp_{50LOC} and Cp_{50INC}) were determined by the response of the previous patient. Target propofol effect site concentrations were increased by 10% if the previous patient responded and decreased by 10% if the previous patient did not respond. Responses to OAA/S and skin incision were assumed to be independent. The concentrations at which 50% of patients lost consciousness (Cp_{50LOC}) and 50% moved to skin incision (Cp_{50INC}) were determined by the up–down method of Dixon[32] by averaging independent crossover pairs for each response. A crossover pair represents a unique set of sequential patients in which the first patient responded and the next patient did not or *vice versa*. Investigators were not blinded to the sevoflurane or propofol dose.

Validation of Propofol Concentrations to Suppress Consciousness and Movement

Our original data for propofol alone Cp_{50LOC}[10] and Cp_{50INC}[9] were obtained using the Duke Computer–Assisted, Continuous–Infusion (CACI) program. This software is no longer available. After Institutional Review Board approval was obtained, an additional 22 patients were recruited to provide five independent, crossover pairs of propofol alone using the STANPUMP algorithm to validate the intercept of propofol alone for isobolographic analysis for Cp_{50LOC} and Cp_{50INC}.[23,33]

Statistical Analysis

Frequency data (sex) were analyzed with chi-square test. The Kruskal-Wallis test was used to detect significant differences in ranked categorical variables such as American Society of Anesthesiologists physical status.

---

§ STANPUMP program. Available at: http://anesthesia.stanford.edu/pkpd. Accessed January 18, 2006.

Isobolographic analysis[33,34] and two-way Student t test were used to compare sevoflurane–propofol patient data to predicted values (simple additivity = half of propofol alone Cp_{50LOC} or Cp_{50INC}). Multifactorial, repeated-measures analysis of variance with *post hoc* Bonferroni test was used to evaluate the significant relations between variable and cofactors (*e.g.*, sex, age, weight) using a standard statistical software package (SPSS version 11; SPSS Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

Results

Thirteen LOC/Cp_{50LOC} and 10 MAC/Cp_{50INC} crossover pairs (12 male and 21 female) were obtained from the 36 patients enrolled in the initial study. Three patients had data collected but participated in neither crossover pair. The average age (mean ± SD) of patients in crossover pairs was 40 ± 9 yr. Average height and weight were 168 ± 13 cm and 74 ± 15 kg, respectively. Average starting noninvasive blood pressure and heart rate were 131 ± 17/72 ± 12 mmHg (systolic/diastolic) and 70 ± 14 beats/min. Preinduction pulse oximetry (100 ± 0%), end-tidal carbon dioxide (34 ± 5 mmHg), and Bispectral Index (96 ± 3) were recorded.

Figure 1 shows the LOC_{50} of sevoflurane–propofol for 13 crossover pairs. Our experimental method examined only a single point on the predicted line of additivity at a single ET_{sevo} (0.46%; 95% confidence interval [CI], 0.45–0.47%). Visually, this result is within the CI of the line of simple additivity (null hypothesis) connecting propofol alone (Cp_{50LOC}) to sevoflurane alone (ET_{sevo}) values on the isobologram.[33] The observed Cp_{50LOC} for propofol at this sevoflurane concentration was 1.2

$\mu g/ml$ (95% CI, 1.1–1.3 $\mu g/ml$) and was not significantly different from the predicted value of 1.5 $\mu g/ml$ (95% CI, 1.2–1.7 $\mu g/ml$) by either isobolographic analysis or two-tailed t test. This analysis had a 90% power to detect a 19% change in propofol dose from predicted.

The isobologram of the corresponding ten MAC/Cp_{50INC} crossover pairs is shown in figure 2. Based on the study of an additional 22 patients (5 crossover pairs), the propofol-alone intercept (Cp_{50INC}) for the isobologram was 10.7 $\mu g/ml$ (95% CI, 10.2–11.3 $\mu g/ml$). The sevoflurane-alone MAC was 1.71% (95% CI, 1.61–1.82%).[8] The observed Cp_{50INC} for propofol was 5.4 $\mu g/ml$ (95% CI, 4.8–6.0 $\mu g/ml$) at an ET_{sevo} of 0.86% (95% CI, 0.85–0.87%). The observed combined propofol–sevoflurane Cp_{50} was not significantly different than that predicted by simple additivity (5.4 $\mu g/ml$; 95% CI, 4.8–5.9 $\mu g/ml$) by either isobologram or two-tailed t test. This analysis had a 90% power to detect a 25% change in propofol dose from predicted.

Responder or nonresponder status was identified in the repeated-measures analysis of variance as a significant covariate for BIS observations. Although there was no significant change in BIS noted before or after OAA/S administration (*data not shown*), mean starting BIS values were significantly higher in patients before test administration in responders (76 ± 12) (OAA/S score ≥ 2, awake) compared with nonresponders (65 ± 9) (table 1). No other hemodynamic or electrophysiologic covariable was statistically significant.

Discussion

There is reason to believe that LOC and movement responses during anesthesia are mediated separately (*via*
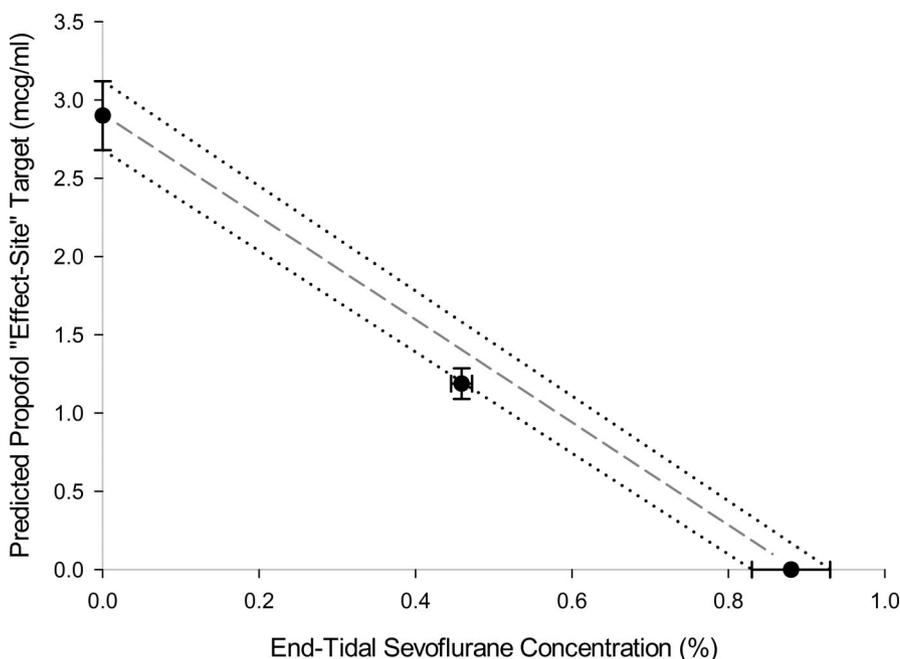
Fig. 1. Loss of consciousness (LOC): isobolographic analysis of propofol and sevoflurane interaction. LOC was defined as loss of response to loud voice with mild prodding (Observer's Assessment of Alertness/Sedation score < 2). The 50% response was determined by averaging crossover pairs following the method of Dixon.[32] Cp_{50LOC} (predicted plasma concentration, ±95% confidence interval) of propofol and LOC_{50} (percent end-tidal concentration) of sevoflurane alone (intercept points) were 2.90 $\mu g/ml$ (2.68–3.12 $\mu g/ml$) and 0.88% (0.83–0.93%),[10] respectively. The line connecting these values graphically represents the line of simple additivity (±95% confidence interval). Our experimental method examined only a single point on the predicted line of additivity for a single end-tidal sevoflurane concentration (0.46%; 0.45–0.47%). The observed Cp_{50LOC} for propofol at this sevoflurane concentration was 1.19 $\mu g/ml$ (95% confidence interval, 1.09–1.29 $\mu g/ml$) and was not significantly different than the predicted value of 1.45 $\mu g/ml$ (95% confidence interval, 1.23–1.67 $\mu g/ml$).

Fig. 2. Isobolographic analysis of propofol and sevoflurane interaction for immobility to surgical incision (minimal alveolar concentration at 50% response [MAC] and/or predicted effect site concentration at 50% response [Cp_{50INC}]). The propofol-alone intercept (Cp_{50INC}) for the isobologram was 10.74 μg/ml (95% confidence interval, 10.20–11.28 μg/ml). The line of simple additivity connects this point to sevoflurane-alone MAC (1.71%; 95% confidence interval, 1.61–1.82%).[8] At an end-tidal sevoflurane concentration of 0.86% (0.85–0.87%), the observed Cp_{50INC} for propofol was 5.39 μg/ml (95% confidence interval, 4.82–5.96 μg/ml) and was not significantly different from that predicted by simple additivity (5.37 μg/ml; 95% confidence interval, 4.83–5.91 μg/ml).
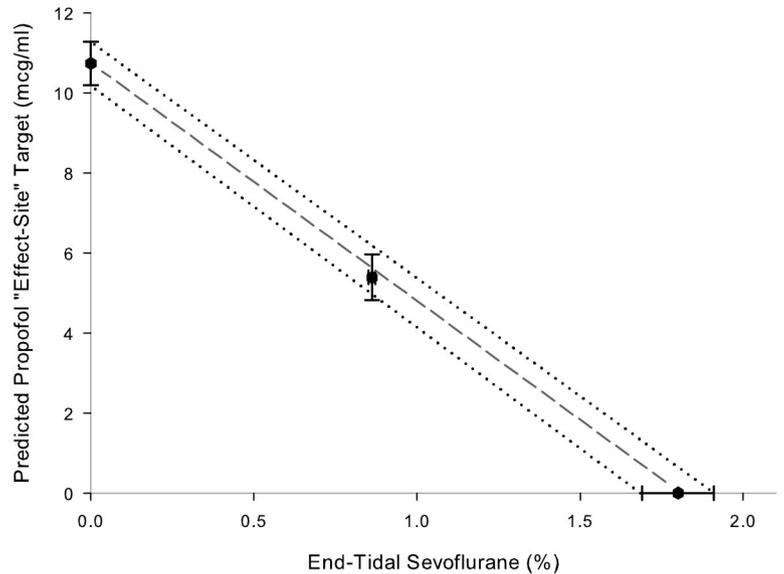
brain and spinal cord, respectively). There are clear data from animal experiments to support these contentions. Rampil *et al.*[2,3] demonstrated that either removing the forebrain or spinal cord transection does not affect MAC. Antognini and Schwartz[4] demonstrated that when only the brain is perfused with volatile anesthetic, the MAC is increased nearly threefold. Therefore, it seems that the brain is not significantly involved in mediating the movement response to noxious stimuli after inhalational anesthesia. Recently, Stabernack *et al.*[35] suggested that immobility produced by an intravenous hypnotic agent (thiopental) in rats seems to be mediated primarily by supraspinal actions, representing a different mechanism of action than that of volatile agents.

This experiment was designed to identify the midpoint on the response surface at a single drug combination of sevoflurane and propofol for LOC and MAC/Cp_{50INC} under conditions approaching steady state. Defining drug–drug interactions depends on precise measurement of the individual drug response and variance (intercept $\pm$ 95% CI of isobologram). CP_{50LOC} with propofol alone (2.9 μg/ml; 95% CI, 2.7–3.1 μg/ml) using STANPUMP target-controlled infusion was identical to the results of Kodaka *et al.*[10] using the CACI[9] system. The definition of

LOC in this study (OAA/S score < 2, no response to mild prodding) was different than many previous reports (OAA/S score < 3, no response to loud voice)[9,36,37] that reported propofol Cp_{50LOC} between 2.1 and 3.3 μg/ml.[10] Our results show simple additivity between sevoflurane and propofol for LOC with no statistical difference between the predicted and observed target propofol effect site concentration at the target sevoflurane concentration. This study had an adequate power (90%) to exclude a type II error and to identify a small change (19%) in propofol effect site concentration. Kodaka *et al.*[10] identified a small statistically significant difference between BIS values at LOC between propofol alone (74 $\pm$ 13) and sevoflurane alone (62 $\pm$ 11). BIS at LOC_{50} for the sevoflurane–propofol crossover pairs in this study (71 $\pm$ 16) was not significantly different from that for propofol-alone (69 $\pm$ 13) controls and was similar to values reported by Kodaka *et al.*[10] Additive drug interactions suggest a common mechanism or a single site of action, whereas synergistic or antagonistic responses suggest separate sites or competing mechanisms of action.[33,38]

Cp_{50INC} for surgical immobility with propofol alone (10.7 μg/ml; 95% CI, 10.2–11.3 μg/ml) obtained in the additional patients enrolled in this study was less than that reported by Smith *et al.*[9] (15.2; 95% CI, 7.6–22.8) and had much less variability. No significant statistical difference between the predicted and observed propofol effect site target concentration with sevoflurane was found. Our results are consistent with simple additivity between sevoflurane and propofol for suppression of movement to incision. Adequate power (90%) was achieved to exclude a type II error and to identify a 25% change in propofol effect site concentration. The average BIS values before MAC were not significantly different between the propofol alone group and for the sevoflurane–propofol combination demonstrating equiv-

Table 1. Bispectral Index in Responders *vs.* Nonresponders with Stimulus-response Testing

	Loss of Consciousness		Surgical Incision	
	Before	After	Before	After
Nonresponder	65 $\pm$ 9	69 $\pm$ 9	21 $\pm$ 6	22 $\pm$ 5
Responder	76 $\pm$ 12*	77 $\pm$ 12	27 $\pm$ 15	28 $\pm$ 19

Data are presented as mean $\pm$ SD. Nonresponders are defined as lack of response to voice plus mild prodding (Observer's Assessment of Alertness/Sedation score < 2) and as lack of movement to skin incision.

* Statistically significant comparison of responder status before loss of consciousness, two-tailed Student *t* test ($P < 0.05$).

alent hypnotic states. No data are available in the literature for BIS at sevoflurane MAC. Poor signal quality, high electrode impedance, or high electromyographic activity did not influence BIS values (data not shown).

It has technically been difficult to study the actions of intravenous anesthetics on end points such as LOC and immobility to painful stimuli because of the difficulty in approximating steady state (equilibrium) drug concentrations at the effect site. In this study, first, we targeted effect site concentrations rather than plasma concentrations. Plasma drug levels are not in equilibrium with brain (LOC) and spinal cord (MAC/Cp_{50INC}) concentrations, making it difficult to control intraindividual and interindividual variables. Second, we allowed sufficient time to elapse (a minimum of 10 min or three distribution half-lives for propofol after predicted effect site drug concentration was reached) to approximate steady state conditions. Third, BIS monitoring directly measures drug effect in the cerebral cortex and provides a method to define equivalent hypnotic states. The BIS values for LOC and skin incision for the drug combination are similar to the available drug-alone values, and no evidence of hypnotic synergism between agents was found.

Issues with the design and interpretation of MAC studies have been raised by several authors.[39,40] The quantal study design used here identifies a population mean effective dose (ED_{50}) based on a single observation per patient (surgical incision). This design has been criticized for ignoring interpatient differences, producing expected errors of 10%, systematically underestimating MAC, and has been characterized as a "giant rat" study.[40,41] Fully defining the interaction of two drugs requires construction of a response surface based on analysis of multiple drug combinations using a continuous measure of response.[23,42] It has been estimated that at least 10 observations per patient are required to obtain an unbiased estimate of the Hill coefficient with the population approach.[42] Lu *et al.*[41] demonstrated that examining quantal responses alone will never establish the concentration-*versus*-response curve. In this study, we chose to maximize the power of the study by using at least 10 crossover observations and to examine only the midpoint of the response surface. It should be noted that the design of this study and other studies using the up–down methodology does not permit blinding and is a limitation of these types of studies.

Although commonly used by clinicians to titrate hypnosis, hemodynamic changes to surgical stimulation are neither sensitive nor specific for awareness or recall during general anesthesia and are poor predictors of both voluntary and involuntary reflexes.[43–45] Before stimulation, no hemodynamic variable was significantly different between patients who responded or did not respond to OAA/S or surgical incision. However, average BIS before OAA/S in nonresponders (LOC or OAA/S score < 2) was significantly lower than that of respond-

ers (table 1), suggesting that a BIS value of 70 or higher was predictive of consciousness (response to loud voice with mild prodding). No difference was found in prestimulus BIS values between patients who moved or did not move to surgical incision.

This study has shown that propofol and sevoflurane produce sedation (LOC) and immobility to surgical stimulation (MAC/Cp_{50INC}) that are predictable from their individual potencies (simple additivity) for each distinct pharmacologic end point. No suggestion of synergistic action between the two anesthetics was found for either response, suggesting that both drugs operate through a common mechanism. This study cannot specifically determine whether the two anesthetics interact at a single site, different drug thresholds at a single site, multiple sites on the same receptor, or on separate receptors producing these two responses. These results are also consistent with the companion article demonstrating additivity at the γ-aminobutyric acid type A receptor for these two agents *in vitro* at clinically relevant concentrations.[29]

References

1. Quasha AL, Eger EI II, Tinker JH: Determination of applications of MAC. ANESTHESIOLOGY 1980; 53:315–34
2. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. ANESTHESIOLOGY 1993; 78:707–12
3. Rampil IJ: Anesthetic potency is not altered after hypothermic spinal cord transection in rats. ANESTHESIOLOGY 1994; 80:606–10
4. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain. ANESTHESIOLOGY 1993; 79:1244–9
5. Rudolph U, Antkowiak B: Molecular and neuronal substrates for general anaesthetics. Nat Rev Neurosci 2004; 5:709–20
6. Campagna JA, Miller KW, Forman SA: Mechanisms of actions of inhaled anesthetics. N Engl J Med 2003; 348:2110–24
7. Katoh T, Ikeda K: The effects of fentanyl on sevoflurane requirements for loss of consciousness and skin incision. ANESTHESIOLOGY 1998; 88:18–24
8. Mapleson WW: Effect of age on MAC in humans: A meta-analysis. Br J Anaesth 1996; 76:179–85
9. Smith C, McEwan AI, Jhaveri R, Wilkinson M, Goodman D, Smith LR, Canada AT, Glass PS: The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. ANESTHESIOLOGY 1994; 81:820–8
10. Kodaka M, Johansen JW, Sebel PS: The influence of gender on loss of consciousness with sevoflurane or propofol. Anesth Analg 2005; 101:377–81
11. Eger EI II, Xing Y, Laster M, Sonner J, Antognini JF, Carstens E: Halothane and isoflurane have additive minimum alveolar concentration (MAC) effects in rats. Anesth Analg 2003; 96:1350–3
12. Murray DJ, Mehta MP, Forbes RB: The additive contribution of nitrous oxide to isoflurane MAC in infants and children. ANESTHESIOLOGY 1991; 75:186–90
13. Murray DJ, Mehta MP, Forbes RB, Dull DL: Additive contribution of nitrous oxide to halothane MAC in infants and children. Anesth Analg 1990; 71:120–4
14. Stevens WD, Dolan WM, Gibbons RT, White A, Eger EI, Miller RD, de Jong RH, Elashoff RM: Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. ANESTHESIOLOGY 1975; 42:197–200
15. Christensen LQ, Bonde J, Kampmann JP: Drug interactions with inhalational anaesthetics. Acta Anaesthesiol Scand 1993; 37:231–44
16. Vinik HR, Bradley EL Jr, Kissin I: Isobolographic analysis of propofol-thiopental hypnotic interaction in surgical patients. Anesth Analg 1999; 88:667–70
17. Vinik HR, Bradley EL Jr, Kissin I: Triple anesthetic combination: Propofol-midazolam-alfentanil. Anesth Analg 1994; 78:354–8
18. Tverskoy M, Fleyshman G, Bradley EL Jr, Kissin I: Midazolam-thiopental anesthetic interaction in patients. Anesth Analg 1988; 67:342–5
19. Peden CJ, Cloote AH, Stratford N, Prys-Roberts C: The effect of intravenous dexmedetomidine premedication on the dose requirement of propofol to induce loss of consciousness in patients receiving alfentanil. Anaesthesia 2001; 56:408–13
20. McClune S, McKay AC, Wright PM, Patterson CC, Clarke RS: Synergistic interaction between midazolam and propofol. Br J Anaesth 1992; 69:240–5

21. Kissin I, Vinik HR, Bradley EL: Midazolam potentiates thiopental sodium anesthetic induction in patients. J Clin Anesth 1991; 3:367–70

22. Stone DJ, Moscicki JC, DiFazio CA: Thiopental reduces halothane MAC in rats. Anesth Analg 1992; 74:542–6

23. Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL: Response surface model for anesthetic drug interactions. ANESTHESIOLOGY 2000; 92:1603–16

24. Nelson LE, Guo TZ, Lu J, Saper CB, Franks NP, Maze M: The sedative component of anesthesia is mediated by GABA$_A$ receptors in an endogenous sleep pathway. Nat Neurosci 2002; 5:979–84

25. Reynolds DS, Rosahl TS, Cirone J, O'Meara GF, Haythornthwaite A, Newman RJ, Myers J, Sur C, Howell OA, Rutter AR, Atack J, Macaulay AJ, Hadingham KL, Hutson PH, Belelli D, Lambert JJ, Dawson GR, McKernan R, Whiting PJ, Wafford KA: Sedation and anesthesia mediated by distinct GABA$_A$ receptor isoforms. J Neurosci 2003; 23:8608–17

26. Sonner JM, Antognini JF, Dutton RC, Flood P, Gray AT, Harris RA, Homanics GE, Kendig J, Oser B, Raines DE, Trudell J, Vissel B, Eger EI II: Inhaled anesthetics and immobility: Mechanisms, mysteries, and minimum alveolar anesthetic concentration. Anesth Analg 2003; 97:718–40

27. Zhang Y, Sonner JM, Eger EI II, Stabernack CR, Laster MJ, Raines DE, Harris RA: Gamma-aminobutyric acid$_A$ receptors do not mediate the immobility produced by isoflurane. Anesth Analg 2004; 99:85–90

28. Gyulai FE, Mintun MA, Firestone LL: Dose-dependent enhancement of *in vivo* GABA$_A$-benzodiazepine receptor binding by isoflurane. ANESTHESIOLOGY 2001; 95:585–93

29. Sebel LE, Richardson J, Singh SS, Bell SV, Jenkins A: Additive effects of sevoflurane and propofol on GABA$_A$ receptor function. ANESTHESIOLOGY 2006; 104:1176–83

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

31. 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

32. Dixon WJ: The up-and-down method for small samples. Am Statist Assoc J 1965; 60:967–78

33. Tallarida RJ, Porreca F, Cowan A: Statistical analysis of drug-drug and site-site interactions with isobolograms. Life Sci 1989; 45:947–61

34. Kissin I: Interactions of intravenous anaesthetics: General principles. Anaesth Pharmacol Rev 1995; 3:90–101

35. Stabernack C, Zhang Y, Sonner JM, Laster M, Eger EI II: Thiopental produces immobility primarily by supraspinal actions in rats. Anesth Analg 2005; 100:128–36

36. Higuchi H, Adachi Y, Dahan A, Olofsen E, Arimura S, Mori K, Satoh T: The interaction between propofol and clonidine for loss of consciousness. Anesth Analg 2002; 94:886–91

37. Fechner J, Ihmsen H, Hatterscheid D, Schiessl C, Vornov JJ, Burak E, Schwilden H, Schuttler J: Pharmacokinetics and clinical pharmacodynamics of the new propofol prodrug GPI 15715 in volunteers. ANESTHESIOLOGY 2003; 99:303–13

38. Tallarida RJ: Drug synergism: Its detection and applications. J Pharmacol Exp Ther 2001; 298:865–72

39. Sonner JM: Issues in the design and interpretation of minimum alveolar anesthetic concentration (MAC) studies. Anesth Analg 2002; 95:609–14

40. Sani O, Shafer SL: MAC attack? ANESTHESIOLOGY 2003; 99:1249–50

41. Lu W, Ramsay JG, Bailey JM: Reliability of pharmacodynamic analysis by logistic regression: Mixed-effects modeling. ANESTHESIOLOGY 2003; 99:1255–62

42. Short TG, Ho TY, Minto CF, Schnider TW, Shafer SL: Efficient trial design for eliciting a pharmacokinetic-pharmacodynamic model-based response surface describing the interaction between two intravenous anesthetic drugs. ANESTHESIOLOGY 2002; 96:400–8

43. Zbinden AM, Petersen-Felix S, Thomson DA: Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia: II. Hemodynamic responses. ANESTHESIOLOGY 1994; 80:261–7

44. Leslie K, Sessler DI, Smith WD, Larson MD, Ozaki M, Blanchard BS, Crankshaw DP: Prediction of movement during propofol/nitrous oxide anesthesia: Performance of concentration, electroencephalographic, pupillary, and hemodynamic indicators. ANESTHESIOLOGY 1996; 84:52–63

45. Dutton RC, Smith WD, Smith NT: Wakeful response to command indicates memory potential during emergence from general anesthesia. J Clin Monit 1995; 11:35–40