Bispectral index and regional cerebral oxygen saturation during propofol/N₂O anesthesia

[L'index bispectral et la saturation en oxygène du sang cérébral régional pendant l'anesthésie au propofol/N₂O]

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Purpose: A study was undertaken to compare the influence of midazolam, isoflurane, and aminophylline (which may antagonize anesthetic action) on bispectral index (BIS) and regional cerebral oxygen saturation (rSO₂) during propofol/N₂O anesthesia, and to test the hypothesis that the drug-induced changes in BIS values are accompanied by a change in rSO₂.

Methods: General anesthesia was administered to 36 patients with a continuous infusion of propofol to maintain a BIS value of 40 ± 5. After baseline recordings, patients were randomly assigned to receive either midazolam, isoflurane, or aminophylline. Bispectral index values, rSO₂ using near-infrared spectroscopy, and hemodynamic parameters were recorded for 60 min.

Results: Midazolam (0.05 mg·kg⁻¹) significantly decreased the BIS from 47.8 ± 5.4 to 35.0 ± 4.5 at five minutes after injection ($P < 0.001$ vs control) during propofol anesthesia, whereas the rSO₂ was unchanged. Similarly, isoflurane (1.1% end-tidal) decreased the BIS from 42.5 ± 7.5 to 27.8 ± 6.9 ($P < 0.001$) without affecting rSO₂. In contrast, aminophylline (3 mg·kg⁻¹) was associated with an increase in BIS from 41.6 ± 2.1 to 48.3 ± 9.2 at five minutes after injection ($P < 0.05$) without affecting rSO₂.

Conclusions: Midazolam or isoflurane-induced decreases in the BIS during propofol anesthesia were not accompanied by a decrease in rSO₂. Aminophylline significantly increased the BIS score during propofol anesthesia, suggesting that aminophylline can antagonize, at least in part, the sedative actions of propofol.

Objectif: Comparer l'influence du midazolam, de l'isoflurane et de l'aminophylline (qui peut contrer l'action anesthésique) sur l'index bispectral (BIS) et la saturation en oxygène du sang cérébral régional (rSO₂) pendant l'anesthésie au propofol/N₂O, et vérifier si les modifications du BIS, induites par le médicament, sont accompagnées d'un changement dans la rSO₂.

Méthode: L'anesthésie générale a été administrée à 36 patients avec une perfusion continue de propofol pour maintenir une valeur de BIS de 40 ± 5. Les mesures de base enregistrées, les patients ont reçu au hasard du midazolam, de l'isoflurane ou de l'aminophylline. Le BIS, la rSO₂ par spectroscopie en proche infrarouge et l'hémodynamique ont été notés pendant 60 min.

Résultats: Le midazolam (0,05 mg·kg⁻¹) a significativement réduit le BIS de 47,8 ± 5,4 à 35,0 ± 4,5 cinq minutes après l'injection ($P < 0,001$ vs témoin) pendant l'anesthésie au propofol, tandis que la rSO₂ n'a pas changé. De même, l'isoflurane (télé-expiratoire, 1,1 %) a diminué le BIS de 42,5 ± 7,5 à 27,8 ± 6,9 ($P < 0,001$) sans affecter la rSO₂. Par ailleurs, l'aminophylline (3 mg·kg⁻¹) a été associée à une augmentation du BIS de 41,6 ± 2,1 à 48,3 ± 9,2 cinq minutes après l'injection ($P < 0,05$) sans affecter la rSO₂.

Conclusion: Les baisses du BIS induites par le midazolam ou l'isoflurane pendant l'anesthésie au propofol n'étaient pas accompagnées d'une baisse de la rSO₂. Cependant l'aminophylline a significativement augmenté le score du BIS, laissant croire qu'elle peut contrer, du moins en partie, les actions sédatives du propofol.

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THE bispectral index (BIS) was created using a concurrent collection of electroencephalograms (EEG) and clinical data from large numbers of patients anesthetized with various agents, from which a Fourier analysis followed by a bispectral calculation was performed.^{1,2} Bispectral index allows monitoring of various factors that influence the patient's central nervous system response. Inhalational anesthetics and propofol produce dose-dependent depression of the BIS value, and the BIS correlates the level of consciousness with a single anesthetic drug. For example, Glass *et al.*³ have reported that the BIS inversely correlates with the end-tidal isoflurane concentration, up to 1.0%, and that propofol-induced loss of consciousness occurred in 95% of patients at a BIS value of 50. In addition, Ibrahim *et al.*⁴ assessed the ability of the BIS to predict the depth of sedation-anesthesia with sevoflurane, propofol and midazolam.

Volatile anesthetics or analgesics are often co-administered during propofol anesthesia in various clinical settings. It is therefore important to understand the impact of the interaction between these drugs in terms of anesthetic depth. For example, Iselin-Chaves *et al.*⁵ examined the effects of the interaction of propofol and alfentanil on recall or loss of consciousness, and found that the sedation and changes in memory function produced by propofol, but not by alfentanil, correlate well with changes in BIS. However, one side effect of co-administered general anesthetics is hypotension, which may result in decreased cerebral blood flow. To examine this influence, cerebral oximetry based on near-infrared spectroscopy (NIRS) has also been used for non-invasive monitoring of regional cerebral oxygen saturation (rSO₂) during general anesthesia. The changes of rSO₂ may reflect changes of cerebral blood flow relative to metabolic rate in the brain. The interaction between propofol and volatile anesthetics on rSO₂ remains unclear.

Several lines of evidence suggest aminophylline may antagonize the sedative action of diazepam and change the depth of anesthesia.⁶⁻⁸ Stirt⁶ first reported the possibility of antagonistic actions of aminophylline on diazepam sedation. Niemand *et al.*^{7,8} suggested the possibility of the involvement of an adenosine receptor blockade of GABA(A) receptors in the antagonistic actions of aminophylline. In addition, as observed during diazepam sedation, Taylor *et al.*⁹ presented a case report of a patient with asthma for whom the infusion rate of propofol required for sedation apparently decreased after disconnection of aminophylline. This case suggests that aminophylline may have similar antagonistic actions on propofol. However, the effects

of aminophylline on the BIS and cerebral oxygenation during propofol anesthesia have not been described.

We therefore undertook a study to compare the effects of midazolam, isoflurane, and aminophylline (which may modulate the GABA receptor function leading to the changes in anesthetic depth during propofol anesthesia) on BIS scores and rSO₂. We also examined whether or not aminophylline would antagonize propofol action on the BIS, and further, tested the hypothesis that drug-induced changes in the BIS score are accompanied by a change in the rSO₂ during propofol anesthesia.

Methods

Patients

After obtaining local Research Ethics Committee approval and written informed consent, 36 American Society of Anesthesiologists I–II status adult patients, between 20 and 65 yr of age, undergoing elective minor surgery were enrolled in this study. Excluded were patients with a body mass index greater than 30 kg·m⁻², anemia (hemoglobin < 10.0 g·dL⁻¹), a history of neurological diseases, and/or use of psychoactive medications.

Study protocol

Patients were randomly allocated by random number tables into one of three groups: the midazolam group, the isoflurane group, and the aminophylline group. No sedative premedication was given before general anesthesia. In the operating room, two 18-G cannulae were inserted into a large forearm vein under local anesthesia; one for drug administration and the other for fluid or blood infusion. Lactated Ringer's solution was infused at a rate of 5 to 10 mL·kg⁻¹·hr⁻¹. Routine physiological monitoring was initiated including an electrocardiogram, non-invasive arterial blood pressure, heart rate, SpO₂, end-tidal CO₂ concentration, end-tidal isoflurane concentration, and body temperature. A radial artery catheter was inserted with local anesthesia for monitoring arterial blood pressure. In some cases, an epidural catheter was also inserted before induction of anesthesia for postoperative analgesia, but epidural injection of local anesthetics or opioids occurred only after the study was complete.

The BIS index was monitored and recorded continuously using the Aspect EEG monitor (A-1050, Aspect Medical Systems, Newton, MA, USA) containing software revision 1.30 in the standard montage. Following alcohol cleaning, disposable BIS sensor electrodes (BIS sensor plus, Aspect Medical Systems, Newton, MA, USA) were applied to the forehead of patients to record the pre-induction value. Impedance

of the electrodes was confirmed to be less than 500 Ω . In addition, continuous, non-invasive monitoring of rSO_2 was also performed using NIRS (OM-200 version 3.17, Shimadzu Corporation, Kyoto, Japan). Changes of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) were measured using wavelengths of 780 and 830 nm. The reflected beam of light was analyzed and data stored continuously on a personal computer. A sampling interval of 0.5 sec was used and $rSO_2 = \text{oxy-Hb} / (\text{oxy-Hb} + \text{deoxy-Hb})$ were calculated. A previous study¹⁰ reported that, among many factors, patient age, hemoglobin concentration, and sensor location may affect rSO_2 values, and thus in all patients the rSO_2 sensors were applied on the right forehead, 3 cm away from the midline to avoid distortion from the sagittal sinus.

Routine physiological monitoring was started and baseline values recorded while the patient breathed 100% oxygen. After breathing 100% oxygen for at least three minutes through a facemask, general anesthesia was induced with a single dose of propofol (2 mg·kg⁻¹ *iv*). To facilitate tracheal intubation, vecuronium bromide (0.1 mg·kg⁻¹) was injected immediately after loss of consciousness (eyelash reflex) occurred. Tracheal intubation was attempted only when the BIS value reached < 40; if the BIS score did not reach 40, an additional single dose of propofol (0.2 mg·kg⁻¹ *iv*) was injected. After intubation, general anesthesia was maintained with oxygen (33%), nitrous oxide (67%), and a continuous infusion of propofol using an infusion pump to maintain mean values of the BIS within the target range 40 $\pm$ 5 before the study period. The propofol infusion was allowed to run at a constant level throughout the study period. Ventilation was controlled to maintain end-tidal PaCO₂ at approximately 35 mmHg. The studies were conducted immediately following induction or after the surgical procedure, to avoid the effects of surgical stimuli on the drug-induced changes of the BIS score. During surgery, supplemental fentanyl and vecuronium were administered as required, but both drugs were avoided during the period of data collection to minimize their effects on the BIS.

After recording baseline values, midazolam (0.05 mg·kg⁻¹ *iv*), or aminophylline (3 mg·kg⁻¹, *iv*) was administered. The selected drug doses were considered standard doses for sedation or anti-asthmatic treatment, respectively. In the isoflurane group, application began when the end-tidal concentration of 1.1% (1.0 MAC) was attained. Physiological data and BIS values were recorded and analyzed before injection, at one minute, and every five minutes after injection. No vasopressor or vasodilator medications were

TABLE I Demographic data

	Midazolam	Isoflurane	Aminophylline
<i>n</i>	12	10	12
Age (yr)	41.7 $\pm$ 14.1	40.4 $\pm$ 18.2	31.4 $\pm$ 13.6
Body weight (kg)	53.0 $\pm$ 5.1	54.4 $\pm$ 14.7	50.6 $\pm$ 17.7
Male/female (<i>n</i>)	1/11	1/11	1/9
Duration of anesthesia (min)	252.1 $\pm$ 97.5	294.1 $\pm$ 158.8	244.3 $\pm$ 139.4
Duration of surgery (min)	183.1 $\pm$ 94.9	214.1 $\pm$ 141.2	176.6 $\pm$ 130.1
Type of surgery	Hysterectomy 7 Adhesiotomy 2 Gastrectomy 1 Others 2	Mastectomy 3 Hysterectomy 4 Thyroidectomy 1 Others 2	Hysterectomy 4 Mastectomy 1 Adhesiotomy 1 Others 6
Dose of propofol (mg·kg ⁻¹ ·hr ⁻¹)	6.5 $\pm$ 1.2	6.9 $\pm$ 1.6	7.4 $\pm$ 1.1 (mg)
Dose (mg) or end-tidal concentration (%)	3.0 $\pm$ 0.8 (mg)	1.2 $\pm$ 0.1 (%)	109.4 $\pm$ 39.9 (mg)

Data are expressed as means $\pm$ standard deviation. There was no significant difference in age, body weight, and dose of propofol between groups.

administered during the study period. However, when systolic blood pressure increased above 140 mmHg or decreased below 80 mmHg during the study period, nicardipine or phenylephrine were administered to treat hemodynamic changes, and the case was excluded from further analysis. All BIS values reflect the mean of three consecutive measurements taken at each data point. All measurements were made by the investigator blinded to the study drugs.

Statistics

Using an expected difference of 5% for the BIS value at five minutes following injection, a variability of 17.7 for BIS values with a power of 0.8 ($\beta = 0.8$) and assuming an $\alpha = 0.05$, it was estimated that 12 patients per group would be required to demonstrate a clinically important difference (Sample Power 2.0, SPSS Inc., Chicago, IL, USA). These figures were based on results of our preliminary study. All data are expressed as mean $\pm$ standard deviation. Statistical analysis was performed using StatMate version III for Windows (ATMS Co., Ltd., Tokyo, Japan). Statistical difference was analyzed by one-factor repeated measures ANOVA followed by the Tukey's method as a post hoc test for each group. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics are shown in Table I. Two patients in the isoflurane group were excluded from analysis, since phenylephrine was used to treat hemo-

FIGURE 1 The effects of midazolam on the bispectral index (BIS) during propofol anesthesia. After baseline data recordings, midazolam ($0.05 \text{ mg}\cdot\text{kg}^{-1}$) was administered intravenously. Midazolam significantly decreased the BIS ($P < 0.001$) and the depression lasted for 25 min. Data are expressed as mean $\pm$ standard deviation.

FIGURE 2 The effects of isoflurane on the bispectral index (BIS) during propofol anesthesia. After baseline data was obtained, isoflurane (1.1%, 20 min) inhalation was started. Isoflurane produced a significant decrease in the BIS ($P < 0.001$). Bispectral index returned to the baseline values within five minutes. Data are expressed as mean $\pm$ standard deviation.

dynamic changes. As a result, the data from 34 patients was analyzed for this study. No significant differences were observed with respect to age, weight, and other parameters among groups. The baseline, non-medicated BIS values of the three groups were between 97–98, with no significant differences among groups. The mean infusion rate of propofol

FIGURE 3 The effects of aminophylline on bispectral index (BIS) during propofol anesthesia. After aminophylline ($3 \text{ mg}\cdot\text{kg}^{-1}$) injection, BIS values increased transiently ($P < 0.05$ vs control). In addition, aminophylline administration was associated with an increase in heart rate ($P < 0.01$) without affecting systolic blood pressure. Data are expressed as mean $\pm$ standard deviation.

before administration of the study drug was $6.9 \pm 1.3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ ($n = 34$). There was no significant difference in the infusion rates of propofol in the three groups.

Midazolam ($0.05 \text{ mg}\cdot\text{kg}^{-1}$) significantly decreased BIS from 47.8 ± 5.4 to 35.0 ± 4.5 at five minutes after injection ($P < 0.001$ vs control, Figure 1) during propofol anesthesia. A significant decrease in the BIS was observed for 30 min after injection. As shown in Table II, rSO_2 was not affected by midazolam injection during propofol anesthesia, i.e., 70.3 ± 7.9 before midazolam and 68.8 ± 7.0 at 20 min after injection. No changes in other parameters such as systolic blood pressure, heart rate, SpO_2 , body temperature, or EtCO_2 after midazolam injection were detected (Table II).

Isoflurane (1.1%, 20 min) significantly decreased the BIS from 42.5 ± 7.5 to 27.8 ± 6.9 ($P < 0.001$ vs control, Figure 2) whereas rSO_2 was unchanged (Table II). The BIS returned to baseline level within ten minutes after isoflurane discontinuation. Systolic blood pressure was also significantly decreased after the introduction of 1 MAC isoflurane at five, ten, 15, and 20 min (Table II). No changes in other parameters such as heart rate, SpO_2 , body temperature, or EtCO_2 during isoflurane application were detected (Table II).

In contrast, aminophylline ($3 \text{ mg}\cdot\text{kg}^{-1}$) transiently but significantly increased BIS from 41.6 ± 2.1 to 48.3 ± 9.2 at five minutes after injection ($P < 0.05$,

TABLE II Hemodynamic and regional cerebral oxygen changes associated with midazolam, isoflurane, aminophylline during propofol anesthesia

	Control	1 min	5 min	10 min	15 min	20 min	25 min	30 min
SBP								
Midazolam	112.0 ± 16.8	112.3 ± 14.6	109.2 ± 15.1	113.1 ± 12.2	115.4 ± 18.5	113.3 ± 18.0	111.3 ± 17.6	108.4 ± 27.7
Isoflurane	116.1 ± 16.8	106.6 ± 17.7	104.1 ± 14.6**	103.8 ± 17.8*	98.9 ± 16.4***	96.1 ± 12.4***	107.0 ± 14.0	108.1 ± 17.0
Aminophylline	119.7 ± 9.7	117.5 ± 7.0	114.5 ± 6.3	115.1 ± 9.1	111.6 ± 10.4	109.7 ± 11.3	113.2 ± 14.1	114.0 ± 12.6
HR								
Midazolam	65.6 ± 13.0	68.0 ± 15.8	70.3 ± 11.6	71.3 ± 11.0	71.3 ± 12.1	69.9 ± 12.5	69.8 ± 12.5	70.9 ± 13.3
Isoflurane	75.4 ± 15.8	81.7 ± 17.0	77.6 ± 16.8	79.3 ± 16.7	79.8 ± 15.4	79.2 ± 16.7	77.5 ± 15.0	80.8 ± 14.2
Aminophylline	74.0 ± 17.9	76.5 ± 19.7	81.1 ± 19.0**	77.5 ± 19.3	77.7 ± 19.8	76.4 ± 19.7	76.7 ± 27.2	73.8 ± 22.0
SpO ₂ (%)								
Midazolam	98.5 ± 1.3	98.6 ± 1.2	98.7 ± 1.3	98.7 ± 1.3	98.7 ± 1.3	98.7 ± 1.3	98.7 ± 1.3	98.7 ± 1.3
Isoflurane	98.9 ± 1.4	99.4 ± 1.1	98.8 ± 1.5	98.8 ± 1.2	98.7 ± 1.3	98.8 ± 1.3	98.8 ± 1.1	99.3 ± 1.1
Aminophylline	98.8 ± 1.3	98.8 ± 1.3	98.9 ± 1.4	98.4 ± 1.1	98.9 ± 1.1	98.9 ± 1.1	99.5 ± 0.6	99.2 ± 0.8
rSO ₂ (%)								
Midazolam	65.4 ± 8.4	65.5 ± 8.5	65.6 ± 7.3	65.5 ± 7.9	64.9 ± 7.4	64.5 ± 7.8	64.3 ± 7.0	64.9 ± 7.1
Isoflurane	73.0 ± 6.9	73.6 ± 8.2	72.6 ± 6.4	72.8 ± 6.5	72.3 ± 4.9	72.7 ± 5.0	71.3 ± 4.4	72.6 ± 6.9
Aminophylline	71.0 ± 5.8	72.7 ± 5.8	70.3 ± 5.5	71.0 ± 4.6	69.0 ± 7.0	69.0 ± 8.4	68.0 ± 7.5	68.5 ± 8.7

SBP = systolic blood pressure (mmHg); HR = heart rate (beat·min⁻¹); rSO₂ = regional cerebral oxygen saturation. * $P < 0.05$, ** $P < 0.01$ *** $P < 0.01$ vs control. Data are presented as mean ± standard deviation.

Figure 3). In addition, heart rate was significantly increased at five minutes ($P < 0.01$ vs control, Table II). During these procedures, no significant changes in rSO₂, systolic blood pressure, or other parameters were observed (Table II).

Discussion

The key finding of the present study is that midazolam or isoflurane-induced decreases in BIS during propofol anesthesia are not accompanied by a decrease in rSO₂. The second observation is that aminophylline significantly increases BIS without affecting rSO₂ during propofol anesthesia.

There have been few studies examining the interaction of anesthetics on BIS and rSO₂. Lovell *et al.*¹¹ previously compared cerebral oxygenation by NIRS during induction of anesthesia with etomidate, propofol, or thiopental. They reported that etomidate (0.31 mg·kg⁻¹) was associated with a decrease in cerebral oxygenation, whereas propofol (3.1 mg·kg⁻¹) and thiopental (6.4 mg·kg⁻¹) were associated with an increase in cerebral oxygenation. The different effects of *iv* anesthetics on oxygen saturation may be due to the different actions on cerebral blood flow and oxygen consumption; both propofol and thiopental maintain flow-metabolism coupling¹² whereas etomidate is associated with a rapid reduction in cerebral blood flow accompanied by a slower reduction in oxygen consumption.¹³ Iwasaki *et al.*¹⁴ compared the effects of higher doses of sevoflurane (8%) on cerebral blood volume with 5% sevoflurane and propofol on cerebral volume using BIS and NIRS during induc-

tion of anesthesia. Only vital capacity inhalation with 8% sevoflurane produced an increase in cerebral blood volume, suggesting that high concentrations of sevoflurane may be dangerous in patients with elevated intracranial pressure. We found that a single dose of midazolam or 1.1% isoflurane induced changes in BIS during continuous propofol anesthesia are not accompanied by a significant change of rSO₂, suggesting the favourable effects of these drugs with respect to cerebral oxygenation and hemodynamic changes.

Historically, Stirr⁶ first reported in 1981 that aminophylline antagonizes the action of diazepam. Others have reported similar actions of aminophylline on diazepam sedation.^{7,8} In this context, Taylor and Collins⁹ reported a possible interaction between aminophylline and propofol. They described a 24-yr-old patient who required respiratory support in the intensive care unit for the treatment of asthma and persistent intense bronchospasm, using propofol sedation. However, she frequently became agitated during aminophylline administration and, after the discontinuation of aminophylline, the infusion requirements for propofol decreased. These observations suggested that aminophylline may have an antagonistic interaction with propofol. Recently, Turan *et al.*¹⁵ examined the effects of aminophylline on BIS during clinical recovery in patients anesthetized with sevoflurane. They found that the BIS scores were significantly higher after aminophylline (5 mg·kg⁻¹) injection than in the control group, and that recovery time variables such as eye opening time and extubation times were slightly shorter in the aminophylline group.

We found that a single dose of aminophylline ($3 \text{ mg}\cdot\text{kg}^{-1}$) during propofol anesthesia significantly increased BIS and heart rate. These data suggest that aminophylline can antagonize, at least in part, propofol effects on EEG parameters used for BIS score production. Although the mechanism of aminophylline's antagonistic action is unknown, one hypothesis relates to the hemodynamic effects of the drug. Generally, as a drug with an extraction ratio approaching 1, propofol clearance is directly proportional with liver blood flow. The addition of aminophylline would be expected to increase cardiac output due to an increase in heart rate and liver blood flow, and thus reduce propofol concentration. This hypothesis may explain, in part, the observed increase in BIS associated with aminophylline administration. In this context, Ishiyama *et al.*¹⁶ reported that ephedrine $0.1 \text{ mg}\cdot\text{kg}^{-1}$, but not phenylephrine $2 \mu\text{g}\cdot\text{kg}^{-1}$, increases BIS values during general anesthesia with sevoflurane combined with epidural anesthesia. These data support the hypothesis that an increase in heart rate may affect the BIS score.

The dose of aminophylline chosen for the present study was relatively small compared to a previous study¹⁵ for several reasons. The first was to avoid significant tachycardia. Second, aminophylline has been shown to cause epileptic discharges at higher doses. Third, aminophylline is mainly metabolized by the hepatic cytochrome P450 system, thus hepatic dysfunction and heart failure reduce the elimination of aminophylline. Care must be taken with the plasma level of aminophylline in patients with such co-existing disease. Turan *et al.*¹⁵ used a higher bolus dose of aminophylline ($5 \text{ mg}\cdot\text{kg}^{-1}$) to examine its effects on recovery time from sevoflurane anesthesia. However, they used aminophylline after inhalational anesthetic discontinuation, which was a different protocol from the present study. Finally, intraoperative awareness is one of the most serious considerations, since aminophylline has been reported to reverse diazepam's sedative/hypnotic action.^{6,7} Fortunately, no patient showed evidence, or complained of this complication postoperatively in the present study.

Cerebral oxygen saturation using NIRS has been used widely to monitor the relative change in oxidative status of the brain. However, the data requires careful interpretation, since the rSO_2 value may be affected by many factors such as age, hemoglobin concentration, bleeding and transfusion.^{10,17} The patients included in the present study experienced minimal bleeding and required no blood transfusion during the study period, and thus we can exclude the effects of such factors on rSO_2 . Thus, our data suggest that administration of 1 MAC isoflurane during propofol anesthesia has little effect on regional cerebral oxygen status.

One might question the use of nitrous oxide in the present study, since nitrous oxide may affect electroencephalographic variables, including the BIS. We do not know the interaction of nitrous oxide with aminophylline, although evidence to date indicates that N_2O induces endogenous opioid peptide release in the periaqueductal gray area of the midbrain leading to the activation of the descending inhibitory pathways, resulting in modulation of the pain/nociceptive processing in the spinal cord.¹⁸ On the other hand, some studies have shown that the use of N_2O had little influence on the BIS score. For example, Rampil *et al.*² reported in human volunteers that 50% $\text{N}_2\text{O}/\text{O}_2$ had no effect on the BIS and spectral edge frequency, although it significantly increased theta, beta 40–50 Hz, and 70–110 Hz band powers. Similar observations that up to 66% N_2O does not alter the BIS have also been reported.¹⁹ Studies have shown that opioids,²⁰ as well as nitrous oxide, do not affect BIS values when correlated with drug concentrations and clinical responses.

In conclusion, we have shown that midazolam or isoflurane-induced decreases in BIS during propofol anesthesia are not accompanied by a decrease in rSO_2 . A single dose of aminophylline interfered with propofol effects on EEG parameters and increased the BIS score, suggesting that aminophylline can antagonize, at least in part, the sedative actions of propofol.

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