

## Changes in the Auditory Evoked Potentials and the Bispectral Index following Propofol or Propofol and Alfentanil

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**Background:** Midlatency auditory evoked potentials (MLAEP) show graded changes with increasing doses of hypnotics but little change with opioids. The effect of their combination on the MLAEP was evaluated. Also, the bispectral index (BIS) was compared with the ability of MLAEP to correlate with sedation and predict loss of consciousness.

**Methods:** Twenty healthy volunteers were randomly assigned to receive stepped increases in propofol concentration (10 subjects) or propofol plus alfentanil 100 ng/ml (10 subjects). At baseline and at each targeted effect site concentration the mean MLAEP, BIS, measures of sedation, and drug concentration were obtained. The relation among MLAEP, BIS, and sedation score was determined. The prediction probability ( $P_k$ ) was calculated and compared for BIS and MLAEP.

**Results:** The BIS and MLAEP patterns showed significant changes (Pa and Nb decreased in amplitude and increased in latency) with increasing level of sedation ( $P < 0.0001$ ). The BIS correlated better with sedation scores (0.884) than did the MLAEP ( $P < 0.05$ ). Pa and Nb latencies showed the best correlation with sedation levels (0.685 and 0.658, respectively). The addition of alfentanil did not affect the relation between MLAEP and loss of consciousness ( $P > 0.15$ ). The BIS ( $P_k = 0.952$ ) was a better predictor of loss of consciousness than were Pa and Nb amplitude ( $P < 0.05$ ) but were comparable to Pa and Nb latency ( $P_k = 0.869$  and 0.873, respectively).

**Conclusion:** MLAEP changes, like the BIS, correlate well with increasing sedation produced by propofol, and these changes in the MLAEP are independent of the presence of an opioid. Among all the MLAEP parameters, Pa and Nb latencies are the

best predictors of increasing sedation and loss of consciousness. (Key words: Anesthesia; hypnotic; monitoring; opioid.)

MIDLATENCY auditory evoked potentials (MLAEP) have been proposed as monitors of the state of anesthesia. They have been shown to be profoundly affected by hypnotic drugs in a graded, reversible, and non-agent-specific manner<sup>2-10</sup> (decrease in amplitudes and increase in latencies). In these studies, changes in the MLAEP correlated with increasing concentrations of hypnotic drugs. Other studies have attempted to demonstrate a relation between MLAEP changes and the state of consciousness and changes associated with surgical stimulation.<sup>11,12</sup> Opioids in clinically relevant concentrations produce little change in the MLAEP.<sup>13,14</sup> Thus far, no studies have attempted to correlate level of sedation to changes in MLAEP.

Most studies evaluating MLAEP as an indicator of the state of anesthesia have evaluated the effect of single drugs, and little is known about the effect of drug combinations, especially opioids and hypnotic drugs. Although opioids decrease the concentration of propofol required for loss of consciousness, they produce a much larger decrease in the concentration of propofol for suppression of movement at incision.<sup>15,16</sup>

The bispectral index (BIS) is another electroencephalogram (EEG)-derived parameter that has been optimized to correlate with level of sedation and loss of consciousness.<sup>17</sup> The purpose of the present study was to examine the effect of the combination of an opioid, alfentanil, and a hypnotic, propofol, on the MLAEP and compare the changes in MLAEP with increasing sedation and loss of consciousness to that produced in the BIS. In addition, we tested the hypothesis that the administration of alfentanil with propofol should not affect those MLAEP parameters, which measure the hypnotic state of anesthesia, even though alfentanil decreases the propofol concentration required for loss of consciousness.

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## Methods

This was a prospective study conducted in 20 paid healthy male or female volunteers. Institutional review board approval was obtained, and all volunteers gave written informed consent. Those with known neurologic disorders, including current use of anticonvulsant or other psychoactive medications, long-term drug or alcohol use, hypertension, or other serious medical conditions that would interfere with response analysis were excluded. The volunteers were divided in two groups of 10 subjects according to which drug they received: Propofol alone or propofol and alfentanil. These volunteers were also part of two other studies, the results of which have already been published.<sup>17,18</sup>

All volunteers underwent a history and physical examination before being enrolled in the study. All were instructed to take nothing by mouth from midnight the night before the study. On the morning of the study, volunteers had an intravenous catheter inserted for fluid and drug administration. A radial arterial catheter was also inserted to monitor blood pressure and to obtain blood samples for subsequent measurement of drug concentration. The volunteers were also monitored using a standard three-lead electrocardiograph and a peripheral pulse oximeter for SpO<sub>2</sub>. They had nasal prongs to receive oxygen and to monitor end-tidal CO<sub>2</sub> and respiratory rate. An observer monitored respiratory and cardiovascular function and determined the need for interventions such as jaw support to maintain an adequate airway.

EEG signals were acquired using gold cup electrodes applied to the scalp with collodion or cream. Skin impedance was maintained at less than 5 k $\Omega$ . The following leads were recorded: Fp1 and Fp2 using Cz as the reference (channels 1 and 2), two additional frontal locations between the preauricular point and the lateral canthus using "Fpz" as the reference (channels 3 and 4), and a ground electrode. The EEG was recorded continuously using an Aspect A-1000 EEG monitor (Aspect Medical Systems, Natick, MA), which also computed the BIS in real time. This instrument has an amplifier band pass of 0.16–80 Hz, a sample rate of 16,384 samples/s, and multiple artifact rejection criteria that are integrated into the BIS algorithm.<sup>19</sup> Data averaged from the combined bifrontal leads (channels 1 and 2) are presented here, although similar results were obtained from all channels.

The digitized raw EEG and the computed BIS values were recorded using a personal computer and stored in

disk files, along with time-synchronized markers describing all clinical assessments and events. Drug infusion data were also recorded in a similar manner. This allowed a full description of each volunteer's drug delivery history, EEG, and clinical response profile on a minute-by-minute basis.

The recorded EEG was used to compute the most recent version (revision 3.0) off-line. The BIS 3.0 values corresponding to that time immediately (10–30 s) before the start of each clinical assessment were used for the subsequent analysis.

Auditory evoked potentials (AEP) were recorded using the hardware and software package EP Averager Program version 1.3 (Anesthetic Research Unit, Northwick Park Hospital, UK) on an IBM PC clone. Binaural clicks of 0.4 ms duration at a rate of 6.33 Hz and 75 dB above normal hearing threshold were presented through ear phones bilaterally.

Gold cup electrodes were affixed to the scalp at Fpz and bilaterally at the mastoid (linked reference) to record AEP. Impedance of all electrodes was maintained at less than 5 k $\Omega$ . The EEG signals were analog filtered with a bandwidth of 0.5–400 Hz, sampled at 1 kHz, and digitally filtered with a high-pass filter of 25 Hz. Recording began simultaneously with stimulation and continued for 125 ms. Responses to 512 stimuli were averaged together to form each evoked potential tracing. Before measuring the waveforms, additional filtering was applied. A high-pass filter of 25 Hz and three-point smoothing were applied to reduce variability due to noise. Four evoked potentials were collected at baseline (before the administration of any drug) and at each drug infusion level. The amplitudes ( $\mu$ V) and latencies (ms) of the waves V, Pa, and Nb were measured manually using a ruler on printed tracings of AEP by an individual (I.C.) who was blinded to which group the volunteer had been randomized. We measured the amplitude as the height of the peak of the wave from the prestimulus baseline (time zero) of the x-axis and the latencies as its distance from the stimulus artifact. Peak V belongs to the brain stem auditory evoked potentials (BAEP), which demonstrates that auditory stimuli are correctly transduced.<sup>20</sup> If peak V could not clearly be identified, the evoked potential tracing was rejected.

After all monitoring had been instituted, the volunteers were given a 15-min resting period. Thereafter, baseline readings were obtained. (These readings were also performed following drug administration at each target steady state drug level.) These consisted of a BIS score,

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

Response	Score Level
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 or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimulus	0

AEP, measure of sedation, and two arterial blood samples for drug concentration before and after each assessment.

Sedation was measured using the responsiveness component of the Observer Assessment of Alertness and Sedation rating scale (table 1). 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.

The effect of propofol and propofol plus alfentanil on the BIS score, AEP, and level of sedation were evaluated. The intravenous drugs were administered *via* a computer-assisted continuous infusion device to a target effect site concentration.<sup>21</sup> The pharmacokinetic parameters of Gepts *et al.*<sup>22</sup> were used for propofol administration and those of Scott and Stanski<sup>23</sup> were used for alfentanil. The accuracy of these pharmacokinetic parameters has previously been validated.<sup>16,24,25</sup> In every subject, propofol was administered in increasing steps to a target effect site concentration of 1, 2, 4, and 6  $\mu\text{g/ml}$  until volunteers lost consciousness as defined by loss of response to a verbal command. The propofol concentra-

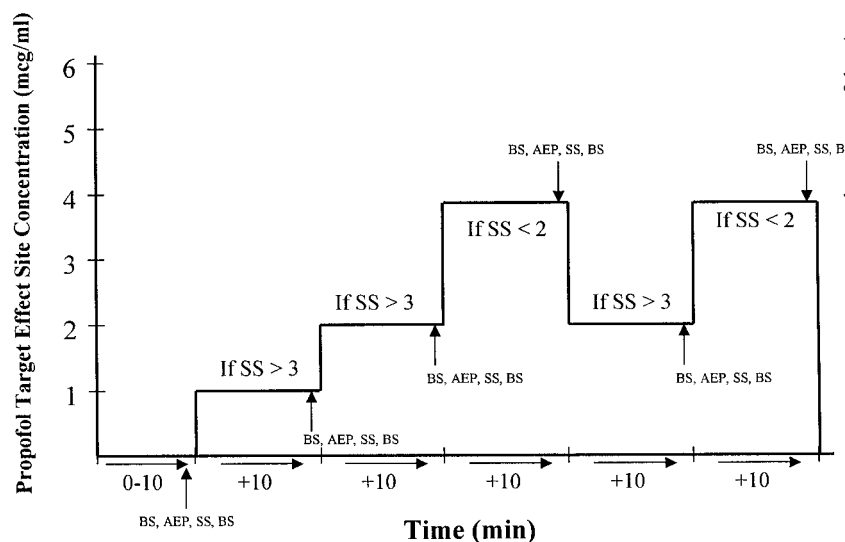
tion was decreased by the same steps until consciousness occurred and then increased and decreased so that at least two crossovers of consciousness-unconsciousness occurred. Alfentanil or placebo (saline) was administered in a double blind fashion to a preselected effect site concentration of 100 ng/ml. At each step, the target concentration was maintained for a minimum of 10 min to permit equilibration with the effect site, as modeled by the propofol and alfentanil ke0<sup>23,26</sup> (fig. 1).

Plasma drug concentrations were determined from the arterial blood samples collected at the beginning and end of each steady state assessment period. The measured concentration at the beginning of each assessment period was used in correlating concentration to MLA<sub>2</sub> or BIS.

Propofol determinations were made using high-pressure liquid chromatography analysis<sup>27</sup> performed at the Anesthesia Research Laboratory at Duke University Medical Center (Durham, North Carolina). The separation and quantification procedures were conducted with a C-18, 15-cm  $\times$  4.6-mm column (Supelcosil LC-18; Supelco, Bellefonte, PA), and detection was fluorometric. Spiked standards (0.5 and 5  $\mu\text{g/ml}$ ) were required to be within 20% of the true value with a coefficient of variability of 12%. The duplicate assays of the participant samples were required to be within 20% of each other.

Plasma samples were measured for alfentanil in duplicate by radioimmunoassay using kits from Janssen Pharmaceutica (Olen, Belgium). The coefficient of variability averaged 11.2% over the range of concentrations encountered in this study.<sup>28</sup>

**Fig. 1. Study design showing the time of arterial blood sampling (BS) for drug concentration determination; measurement of bispectral index (BIS), auditory evoked potentials (AEP), and sedation score (SS); and the adjustment of propofol target effect site concentration according to the sedation level.**



## PROPOFOL/ALFENTANIL ON SEDATION AND AUDITORY EVOKED POTENTIALS

*Statistical Analysis*

The relation among the different evoked potential variables or BIS, measured drug concentration, and sedation level was analyzed using generalized estimating equations.<sup>29</sup> Generalized estimating equations were introduced by Liang and Zeger in 1986 as an extension of generalized linear models to accommodate correlated data using the same link function and linear predictor setup. Generalized estimating equations allow in addition the ability to model the covariance structure of the response measures. It models the first two moments without specifying the complete distribution of the responses. This statistical approach was chosen because it accounts for the within-subject correlation in the face of repeated measurements in the same subject. The effect of the presence of alfentanil was determined by including an indicator (group) in each of the generalized estimating equation models.

Pearson correlations of BIS and AEP variables with sedation and propofol concentration were calculated. Tests for the equality of these correlations for each AEP variable and BIS between the two treatment groups were performed using the Fisher Z transformation. Tests for the equality of these correlations within each group was also done using the single sample test of Olkin.<sup>30</sup> Bonferroni correction was done to account for the multiple testing.

All volunteers who responded to any verbal command (sedation scores 3, 4, and 5) were classified as conscious. Those who did not respond (sedation scores of 0, 1, and 2) were considered to be unresponsive and unconscious. Logistic regression techniques were used to analyze these relations for the quantal endpoints of loss of consciousness. We determined for the plasma concentration of propofol and for the MLAEP variables the values at which 50% and 95% of volunteers were unconscious ( $Cp_{50}$  and  $Cp_{95}$ ;  $Pa$  and  $Nb$  amplitudes<sub>50</sub> and <sub>95</sub> and  $Pa$  and  $Nb$  latencies<sub>50</sub> and <sub>95</sub>, respectively) for each group. The limits corresponding to the 95% confidence intervals surrounding the 50% and 95% probabilities of unconsciousness were calculated.

The prediction probability ( $P_k$ ) as described by Smith *et al.*,<sup>31</sup> was calculated for BIS, MLAEP parameters ( $Pa$  and  $Nb$  latencies and amplitudes), propofol measured, and target concentration and compared within each group using the usual Gaussian test statistic. To enable comparison of  $P_k$  values, we used  $1 - P_k$  when the  $P_k$  value was less than 0.5. Bonferroni corrections were done to account for multiple tests.

**Table 2. Demographics**

Groups	Propofol	Propofol/Alfentanil (100 ng/ml)
Number of subjects	10	10
Mean age $\pm$ SD (yr)	31 $\pm$ 6	31 $\pm$ 7
Mean weight $\pm$ SD (kg)	72 $\pm$ 20	81 $\pm$ 17
Mean height $\pm$ SD (cm)	171 $\pm$ 9	174 $\pm$ 10
Male	5	8
Female	5	2

SD = standard deviation.

Descriptive statistics were used to compare demographic variables between the study groups. Probability values less than 0.05 were considered significant. Statistical analyses were done using the SAS software of SAS Institute (Cary, NC).

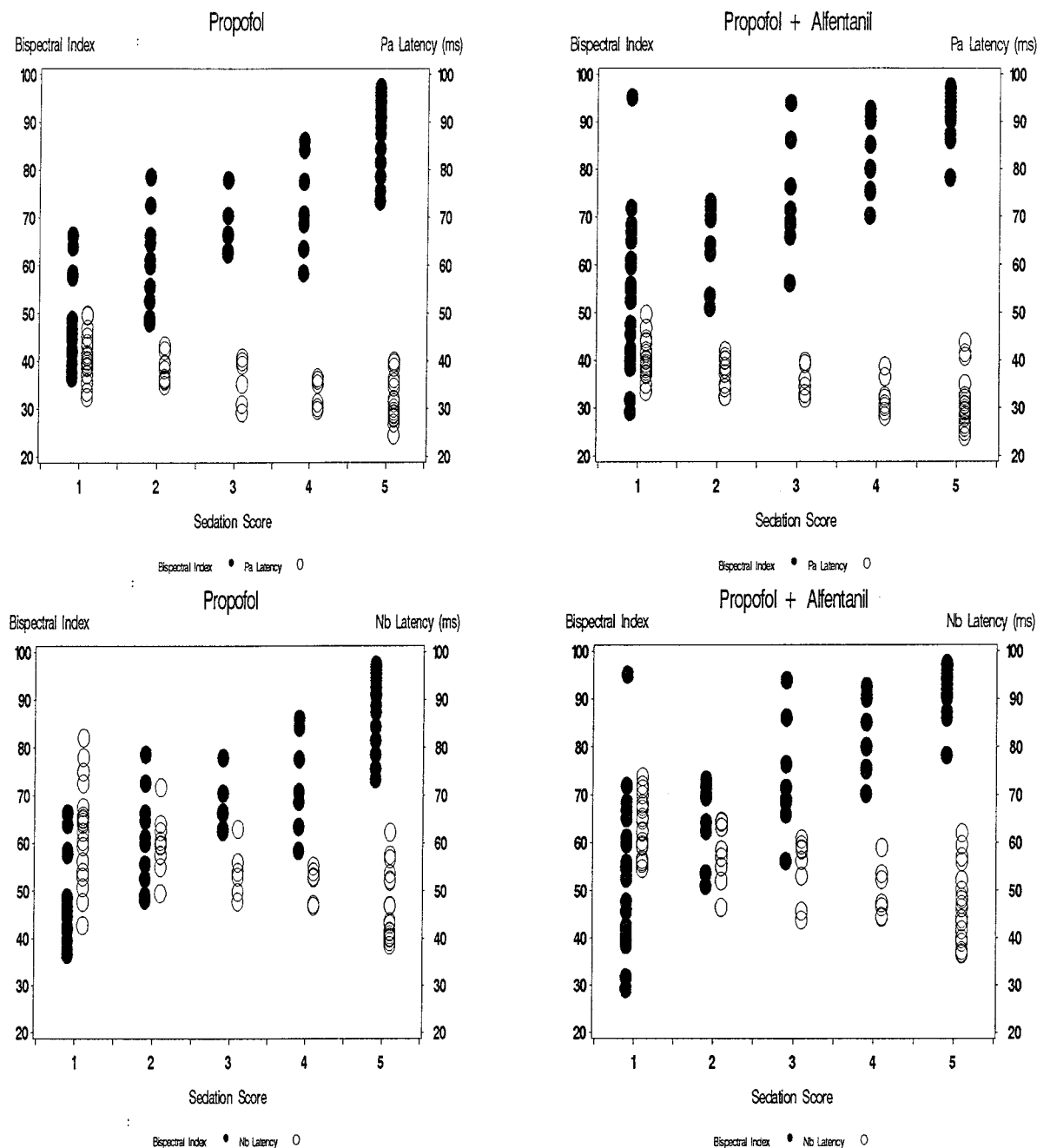
**Results**

There were no statistically significant differences between the two groups with regard to age, weight, height, and gender (table 2). Typical changes in MLAEP with increasing propofol concentration are illustrated in figure 2. Peak V amplitude of the BAEP did not change significantly either with the increase of the plasma propofol concentration ( $P = 0.6$ ) or with increasing level of sedation ( $P = 0.7$ ). Peak V latency was slightly prolonged by both conditions ( $P = 0.03$  with propofol concentration;  $P = 0.015$  with sedation level). All other parameters showed highly significant changes (decrease of BIS index and  $Pa$  and  $Nb$  amplitudes and increase of  $Pa$  and  $Nb$  latencies) with increasing plasma propofol concentrations ( $P < 0.0001$ ) and increasing sedation level ( $P < 0.0001$ ) with and without alfentanil (figs. 3 and 4). These changes were comparable between groups for all AEP parameters analyzed except for  $Pa$  and  $Nb$  amplitudes, which were more pronounced in the group receiving propofol alone.

The BIS index showed a better correlation with propofol concentration ( $P < 0.00005$ ) and sedation level ( $P < 0.000005$ ) than did the MLAEP. This is illustrated in figures 3 and 4, where the relation between change in sedation score and the BIS or MLAEP parameter values are plotted. Among all waveform parameters measured,  $Pa$  and  $Nb$  latency showed the best correlation with propofol concentration and sedation level ( $P < 0.005$ ). MLAEP correlations were comparable between the propofol and propofol-alfentanil groups ( $P > 0.7$ ; tables 3 and 4).



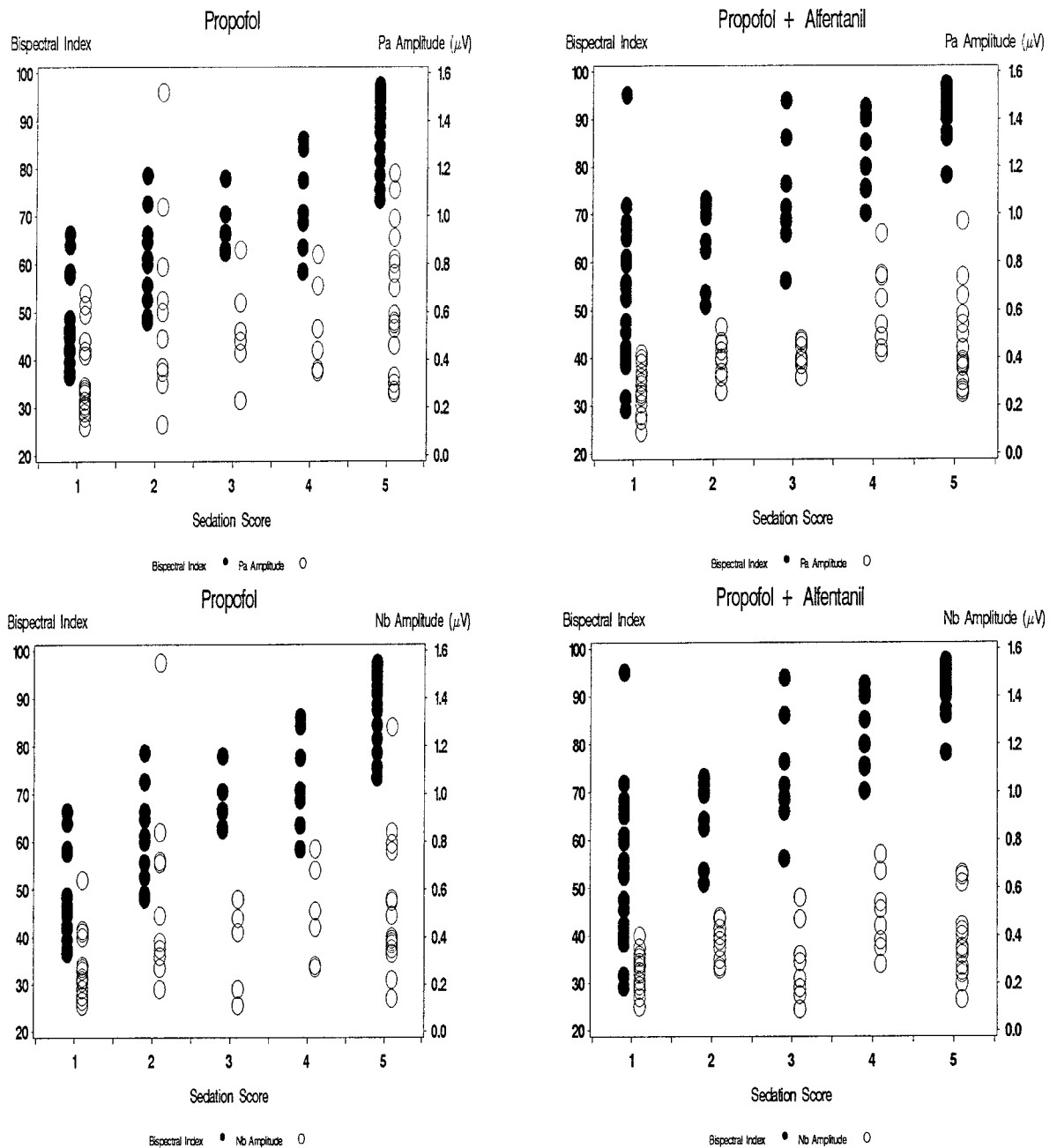
## PROPOFOL/ALFENTANIL ON SEDATION AND AUDITORY EVOKED POTENTIALS



**Fig. 3.** Scatter diagrams of the relation between bispectral index (BIS), Nb and Pb latency (ms), and increasing sedation score as listed in table 1, when volunteers were administered increasing concentrations of propofol or propofol combined with a target alfentanil concentration of 100  $\mu\text{g}/\text{ml}$ .

feature distinguishing these two states.<sup>32</sup> Similar to our study, Newton *et al.* demonstrated that the largest changes accompanying the transition from partial to no response to verbal command (consciousness to unconsciousness) were in Pa and Nb latencies.<sup>33</sup> Schwender *et al.*

*al.* showed that a threshold of Pa latency increase of greater than or less than 12 ms provided a sensitivity of 100% and a specificity of 77% in distinguishing patients with implicit memory from patient without implicit memory postoperatively.<sup>34</sup> In contrast, Heneghan *et al.*<sup>6</sup>



**Fig. 4.** Scatter diagrams of the relation between bispectral index (BIS), Nb and Pb amplitude ( $\mu\text{V}$ ), and increasing sedation score as listed in table 1, when volunteers were administered increasing concentrations of propofol or propofol combined with a target alfentanil concentration of 100  $\mu\text{g}/\text{ml}$ .

compared the slopes of the changes of the MLAEP parameters against minimum alveolar concentration multiples for isoflurane, enflurane, and halothane. They demonstrated that Pa and Nb amplitude were more promising indices of the depth of anesthesia than were Pa and Nb latencies because they were not quantitatively

differently affected by the three volatile agents and were qualitatively similarly affected by etomidate and althesin. Mantzaridis and Kenny derived mathematically from the AEP a single numerical parameter reflecting both amplitudes and frequencies known as the auditory evoked potential index (AEPidx). This index proved to be reli-

## PROPOFOL/ALFENTANIL ON SEDATION AND AUDITORY EVOKED POTENTIALS

**Table 3. Pearson Correlation Coefficients between BIS, Auditory Evoked Potentials Parameters, and Sedation in Both Groups**

	Propofol	Propofol/alfentanil
BIS	0.884*	0.848*
V amplitude	-0.035	0.068
Pa amplitude	0.385	0.486
Nb amplitude	0.328	0.39
V latency	-0.164	-0.361
Pa latency	-0.685†	-0.673§
Nb latency	-0.658‡	-0.725

BIS = bispectral index.

\* Significantly different from all the auditory evoked potentials parameters ( $P < 0.0000005$ , at  $\alpha = 0.002$ ).

† Significantly different from V amplitude and latency, Pa and Nb amplitudes ( $P < 0.001$  at  $\alpha = 0.002$ ).

‡ Significantly different from V amplitude and latency ( $P < 0.001$  at  $\alpha = 0.002$ ).

§ Significantly different from V amplitude ( $P = 0.0003$  at  $\alpha = 0.002$ ).

|| Significantly different from V and Nb amplitude ( $P < 0.00095$  at  $\alpha = 0.002$ ).

able and comparable to Nb latencies in distinguishing consciousness from unconsciousness.<sup>37</sup>

The BIS correlated better than the MLAEP with propofol concentration and sedation level. Similar to our results, Doi et al.<sup>38</sup> found that the BIS correlated better with calculated blood propofol concentration during emergence from anesthesia than did the AEPidx mentioned previously. This would indicate that the MLAEP is a good indicator of the transition between consciousness and unconsciousness but it is less reliable in tracking these states. The BIS is derived from several parameters of the EEG and has been optimized to correlate with increasing sedation. It is therefore not surprising that individual parameters of the MLAEP are not as good in correlating with increasing levels of sedation as the BIS. Additionally, our study revealed that the BIS was a better predictor of loss of consciousness than Pa and Nb amplitude but was comparable to the prediction properties of Pa and Nb latencies. Two studies comparing the AEPidx and the BIS as detectors of awareness showed that the AEPidx was the best at distinguishing the transition from unconsciousness to consciousness.<sup>38,39</sup> The differences between our study and those previously reported are multiple and include the use of an index *versus* the actual MLAEP parameters, the use of different clinical endpoints to define unconsciousness (loss of response to speaking voice *vs.* absence of eye opening to command<sup>38</sup> and loss of response to a verbal command to squeeze the investigator's hand<sup>39</sup>), and the use of different statistical approaches.

The MLAEP changes with the administration of propofol were not affected by the addition of alfentanil. Our results agree with other studies<sup>13,14</sup> showing a preservation of the BAEP and slight changes in the early cortical waves of the MLAEP during administration of high doses of opioids. The MLAEP are the AEP components occurring 10–100 ms after stimulus presentation and originate (mainly Pa) from the primary auditory cortex of the temporal lobe.<sup>40,41</sup> In the presence of high doses of opioids, the auditory stimuli can be transduced and conducted in the brain stem and may be processed in the primary auditory cortex. The auditory input is often described as the last sensory modality to be abolished and the first to return at light level of anesthesia.<sup>42</sup> As there is a parallel between perception of auditory stimuli and consciousness, the absence of effect of opioids on MLAEP can be related to reports of higher incidence of intraoperative awareness when opioids are the primary anesthetic.<sup>43,44</sup>

At present, MLAEP have four inconveniences which may detract from their use in clinical practice. First, they need considerable time to produce a response (0.5–1 min to build up an average for the AEP compared with continuous display of an index for the BIS). A moving time averaging technique described by Davies *et al.*<sup>45</sup> has overcome this problem, allowing a faster response time (every 3 s). Second, difficulties exist in interpreting the waveforms and on-line measurement of Pa and Nb latencies. The AEPidx mentioned previously can now be

**Table 4. Pearson Correlation Coefficients between BIS, Auditory Evoked Potentials, and Propofol Measured Concentration in Both Groups**

	Propofol	Propofol/alfentanil
BIS	-0.8*	-0.74*
V amplitude	-0.111	-0.02
Pa amplitude	-0.533†	-0.438
Nb amplitude	-0.463	-0.337
V latency	0.088	0.102
Pa latency	0.615‡	0.397§
Nb latency	0.627	0.539#

BIS = bispectral index.

\* Significantly different from all the auditory evoked potentials parameters ( $P < 0.00005$  at  $\alpha = 0.002$ ).

† Significantly different from V and Nb amplitude ( $P < 0.0002$  at  $\alpha = 0.002$ ).

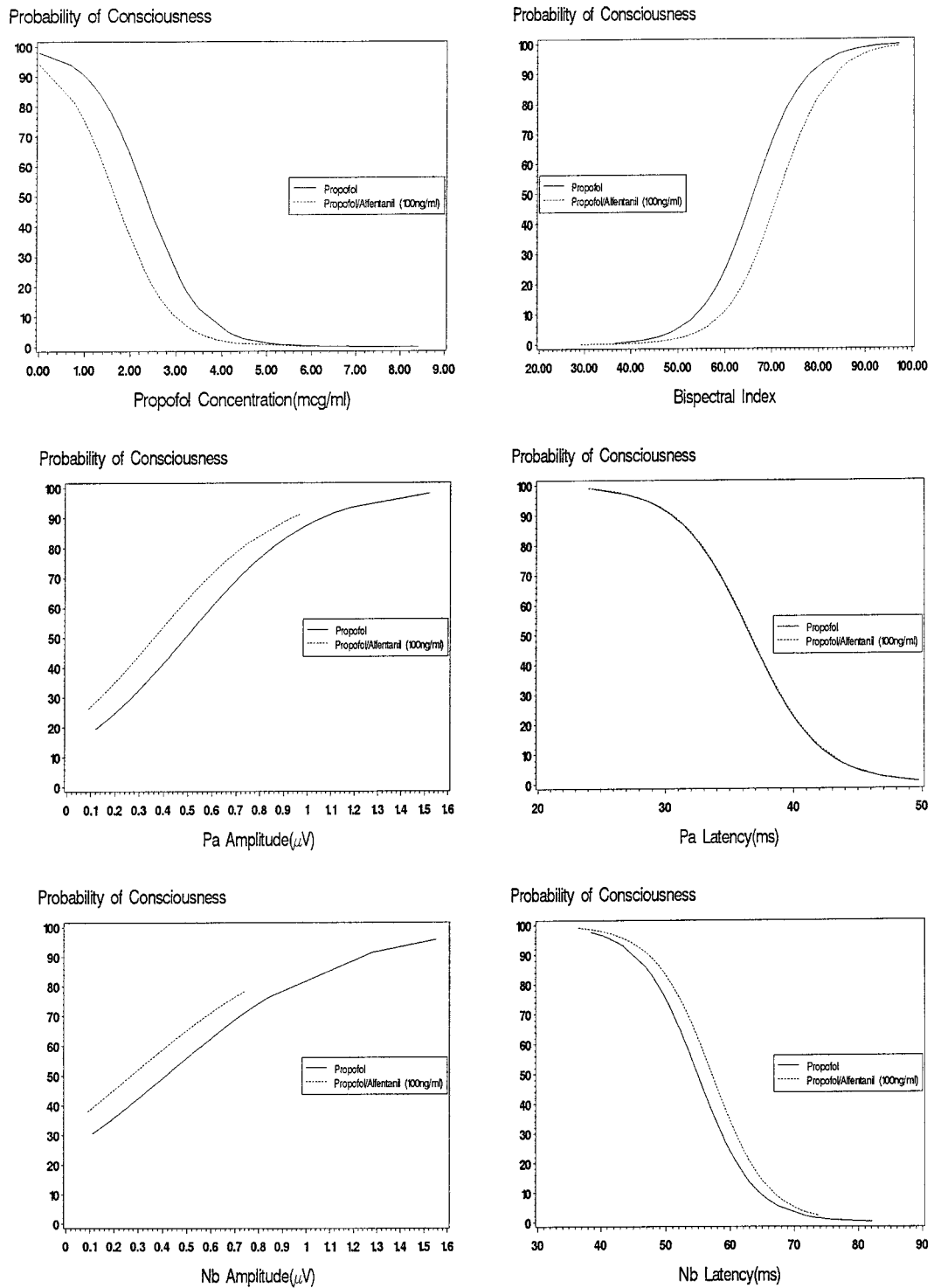
‡ Significantly different from V latency ( $P < 0.001$  at  $\alpha = 0.002$ ).

§ Significantly different from Nb latency ( $P < 0.0005$  at  $\alpha = 0.002$ ).

|| Significantly different from V amplitude and latency ( $P < 0.0005$  at  $\alpha = 0.002$ ).

# Significantly different from Pa latency ( $P < 0.00001$  at  $\alpha = 0.002$ ).





**Fig. 5.** The relation between measured propofol concentration, bispectral index (BIS), Pa amplitude, Nb amplitude, Pa latency, Nb latency, and probability of a positive response (0–100% probability) to verbal command were determined using logistic regression analysis of a quantal endpoint (conscious–unconscious) for all volunteers receiving either propofol alone (solid line) or propofol and alfentanil 100 ng/ml (dotted line).

## PROPOFOL/ALFENTANIL ON SEDATION AND AUDITORY EVOKED POTENTIALS

**Table 5. MLAEP50 and 95, Cp50, and 95 for Loss of Consciousness and Limits Corresponding to the 95% Confidence Intervals for Both Groups**

	Propofol	Propofol/Alfentanil
Pa amplitude 50	0.45 (0.31–0.60)	0.39 (0.26–0.52)
Pa amplitude 95	*	*
Pa latency 50	36.4 (34.55–38.23)	36 (34.18–37.82)
Pa latency 95	45.83 (42.23–49.42)	43.99 (40.84–47.15)
Nb amplitude 50	0.38 (0.19–0.57)	0.3 (0.11–0.49)
Nb amplitude 95	*	*
Nb latency 50	54.5 (51.68–57.64)	56.49 (53.58–59.4)
Nb latency 95	73.57 (66.55–80.71)	69.99 (64.63–75.37)
Cp50	2.25 (1.80–2.69)†	1.63 (1.24–2.02)
Cp95	6.47 (4.77–8.23)†	4.13 (3.09–5.16)

\* These values are not reported because these parameters did not reach the 95% probability of unconsciousness.

† Significantly different between propofol and propofol-alfentanil ( $P = 0.04$ ).

derived on-line. Third, technical difficulties exist in obtaining and recording AEP (set-up time > 5 min). Finally, AEP requires auditory stimuli and therefore is applicable only to patients with preserved hearing. However, based on the data from this study, MLAEP are promising as monitors of increasing sedation and loss of consciousness.

MLAEP changes correlated well with increasing sedation produced by propofol and were not affected by the presence of alfentanil. The BIS correlated better with the level of sedation than any of the MLAEP parameters. Among all the MLAEP, Pa and Nb latencies showed the best correlation with propofol concentration and sedation level and were comparable to the BIS as predictors of loss of consciousness.

**Table 6. Prediction Probability ( $P_k \pm SE$ ) Scores for Correctly Predicting Whether Subjects Were Conscious (OAAS Scores 3–5) or Unconscious (OAAS scores 1–2) in Both Groups**

	Propofol	Propofol/Alfentanil
BIS	0.952 $\pm$ 0.023*	0.937 $\pm$ 0.031†
Pa amplitude	0.729 $\pm$ 0.067	0.780 $\pm$ 0.056
Nb amplitude	0.699 $\pm$ 0.07‡	0.673 $\pm$ 0.067
Pa latency	0.869 $\pm$ 0.044	0.860 $\pm$ 0.046
Nb latency	0.873 $\pm$ 0.045	0.885 $\pm$ 0.039
Propofol measured concentration	0.932 $\pm$ 0.03	0.834 $\pm$ 0.052
Propofol target concentration	0.854 $\pm$ 0.041	0.864 $\pm$ 0.037

BIS = bispectral index.

\* Significantly different from Pa and Nb amplitude ( $P < 0.002$  at  $\alpha = 0.0025$ ).

† Significantly different from Nb amplitude ( $P < 0.0005$  at  $\alpha = 0.0025$ ).

‡ Significantly different from propofol measured concentration ( $P < 0.0025$  at  $\alpha = 0.0025$ ).

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