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The Effect of Ketamine on Human Somatosensory Evoked Potentials and its Modification by Nitrous Oxide

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The effect of ketamine alone and in combination with N_2O (70% inspired) on median nerve somatosensory evoked potentials (SSEPs) was investigated in 16 neurologically normal patients undergoing elective abdominopelvic procedures. The anesthetic regimen consisted of ketamine (2 mg/kg iv bolus followed by continuous infusion at a rate of 30 $\mu g \cdot kg^{-1} \cdot hr^{-1}$), neuromuscular blockade (atracurium), and mechanical ventilation with 100% oxygen. SSEP recordings were obtained immediately preinduction and at 2, 5, 10, 15, 20, and 30 min postinduction. Thereafter, N_2O was added with surgical incision and maintained for 15 min. At 5-min intervals, SSEP recordings were again taken during and after N_2O. With minor exceptions, mean cortical and noncortical latencies as well as noncortical-evoked potential amplitude were unaffected by either ketamine or N_2O. Ketamine induction increased cortical amplitude significantly with maximal increases occurring within 2–10 min. For example, at 5-min postinduction, mean N1-P1 amplitude increased from 2.58 ± 1.05 (baseline) to 2.98 ± 1.20 μV and P1-N2 amplitude increased from 2.12 ± 1.50 (baseline) to 3.99 ± 1.76 μV. Throughout the 30-min period after ketamine induction, mean P1-N2 amplitude increased generally by more (57–88%) than did mean N1-P1 amplitude (6–16%). N_2O added to the background ketamine anesthetic produced a rapid and consistent reduction in both N1-P1 and P1-N2 amplitude. Thus, at 1 min after N_2O, mean N1-P1 amplitude decreased from 2.74 ± 1.11 to 1.64 ± 0.63 μV, while P1-N2 amplitude decreased from 3.32 ± 1.52 to 1.84 ± 0.87 μV. After 15 min of N_2O, these amplitudes remained depressed at 1.35 ± 0.52 and 1.72 ± 0.71 μV, respectively. On elimination of N_2O, cortical amplitudes recovered to within 85–90% of their pre-N_2O level. It is concluded that, when used as the sole anesthetic agent, ketamine enhances the cortical component of the human somatosensory evoked potential. However, when N_2O is introduced, the ketamine enhanced cortical amplitude is reduced by approximately 50%. When judged against the known depressant effect of N_2O, this would suggest that ketamine and N_2O are near additive with respect to their effects on cortical SSEP amplitude. (Key words: Anesthetic gases: nitrous oxide. Anesthetics, intravenous: ketamine. Monitoring, evoked potentials: somatosensory.)

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MANY COMMONLY USED ANESTHETICS affect human somatosensory evoked potentials (SSEPs) by depressing amplitude and prolonging latency to varying degrees. This can interfere with effective recording of SSEPs, especially when it is desirable to monitor the somatosensory cortical evoked potential (SCEP). Only a few anesthetics, such as etomidate and possibly propofol, enhance cortical SCEP amplitude.[1,2] It is conceivable that other anesthetics may have similar properties and could therefore be used to facilitate intraoperative SSEP monitoring. The facilitatory property of ketamine anesthesia on intraoperative SSEPs during correction of scoliosis surgery has been mentioned,§ but systematic data regarding the interaction of ketamine and SSEPs have not previously been reported in humans. In an effort to identify anesthetic regimens with potentially SSEP enhancing properties, we studied the effect of ketamine without as well as with the addition of nitrous oxide (N_2O) on human median nerve SSEPs.

Materials and Methods

With institutional approval and informed consent, 16 neurologically normal patients (25–46 yr) undergoing elective pelvic and abdominal procedures were studied. All patients received lorazepam 2–4 mg po at least 1 h prior to induction. Anesthesia was induced with ketamine (2 mg/kg iv bolus) and maintained by continuous infusion at a rate of 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$, nondepolarizing neuromuscular blockade (atracurium) and 100% oxygen. Intravenous labetolol was administered when blood pressure exceeded 200/100 mmHg. SSEPs were recorded in duplicate immediately preinduction (PRE) and at 2, 5, 10, 15, 20, and 30 min postinduction. Immediately thereafter, N_2O (70% inspired) was added, using a 10 l/min total gas flow, and surgical incision was made. SSEP recordings were continued at 1, 5, 10, and 15 min after N_2O was introduced. N_2O was then discontinued while maintaining a 10 l/min total gas flow for 15 min and SSEPs were again recorded at 5 min intervals. Throughout the study period ventilation was controlled to maintain end-tidal carbon dioxide tension (ET_{CO_2}) between 28 and 32 mmHg. Body temperature was controlled using an in-circuit heater/humidifier. Before as well as after induction, adequate oxygen saturation (>95% by pulse oximetry) was ensured continually.

§ Nielsen GH: Anesthesia for orthopedic surgery in the geriatric patient. Clin Anaesth 4:974, 1986.

TABLE 1. Physiologic Variables (Mean ± SD) after Ketamine

	Postinduction Time						
	PRE	2 min	5 min	10 min	15 min	20 min	30 min
MBP (mmHg)	92 ± 11	110 ± 13*	119 ± 13*	117 ± 10*	114 ± 9*	111 ± 7*	109 ± 10*
HR (b/min)	79 ± 17	92 ± 18*	100 ± 20*	106 ± 18*	102 ± 16*	100 ± 16*	95 ± 18*
T (°C)	—	36.4 ± 0.6	36.4 ± 0.6	36.4 ± 0.6	36.4 ± 0.5	36.5 ± 0.5	36.4 ± 0.5
ET_{CO_2} (mmHg)	—	29 ± 2	31 ± 2	32 ± 3	32 ± 3	31 ± 2	30 ± 2

* $P < 0.01$ *vs.* PRE.

Using a Pathfinder II Electrodiagnostic Monitoring System (Nicolet Biomedical, Madison, WI), SSEPs were elicited by unilateral median nerve stimulation and were simultaneously recorded from surface electrodes (impedance ≤ 3 kOhms) at Erb's point, the second cervical vertebra and the contralateral cortex (C3′ or C4′, International 10-20 System). A constant current stimulus of 200 μs duration was delivered to adhesive electrodes overlying the median nerve at the wrist. The stimulus was applied at an intensity of motor threshold plus 30% and repeated 400 times at a frequency of 3.1 Hz. The signal was recorded over a 40-ms timebase using bandpass filters of 30 and 500 Hz, and was amplified 120,000 times (corresponds to a Pathfinder II sensitivity setting of 50). The waveforms of interest consisted of a negativity at approximately 10 ms (Erb's), 14 ms (Clls), and 19 ms (N1) followed by a positive deflection at approximately 21 ms (P1) and a negative deflection at 26 ms (N2). Trough-to-peak amplitude was measured using the respective waveform peaks immediately following Erb's, Clls, N1, and P1. Central conduction time (CCT) was calculated as the Clls-N1 interlatency difference. Cortical noise amplitude ratios were determined for the PRE, the 2 and 5 min and the 5 and 10 min waveform pairs. This ratio was calculated according to the method described by Nuwer[3] using overlays of successively acquired SCEPs. The numerator consisted of the amplitude of the cortical waveform, while the denominator was measured as the maximum amplitude difference in the nonreproducible sections of the waveform overlays. With each SSEP recording, mean systemic blood pressure (MBP), heart rate (HR), pharyngeal temperature (T), end-tidal CO_2 (ET_{CO_2}), and end-tidal N_2O (ET_{N_2O}) tensions were measured. Care was taken not to cool the stimulated extremity by wrapping it in warm blankets. The data were evaluated using a repeated measures analysis of variance (RM ANOVA) and unpaired *t* tests where appropriate. If the RM ANOVA indicated significant differences among the observation points, the Newman-Keuls procedure for multiple comparisons was employed. Statistical significance was assumed at the $P < 0.05$ level.

Results

MBP, HR, T, ET_{CO_2} and ET_{N_2O} appear in tables 1 and 2. Mean cortical noise amplitude ratios were 4.57 ± 1.54, 3.90 ± 1.61, and 5.03 ± 2.20 at PRE, 2/5 and 5/10 min, respectively. MBP and HR increased significantly after ketamine while other measured physiologic variables remained stable. Only 6/16 patients required labetolol for control of blood pressure. SSEPs were recorded without difficulty throughout the study period. Preinduction SSEP latencies (mean ± SD) were 10.2 ± 0.9 (Erb's), 13.4 ± 1.0 (Clls), 18.6 ± 1.3 (N1), 21.6 ± 1.1 (P1), 26.3 ± 2.8 (N2), and 5.2 ± 0.7 (CCT). With the exception of a minor increase in the Erb's latency, mean cortical and noncortical latencies were unchanged after ketamine and ketamine plus N_2O, as was CCT. SSEP amplitude data appear in tables 3 and 4. N1-P1 amplitude increases induced by ketamine were significant at 2, 5 ($P < 0.01$), and 10 ($P < 0.05$) min after induction. In 4/16 patients N1-P1 amplitude decreased and individual amplitude increments in the remaining patients ranged from 4–73% at 5 min,

TABLE 2. Physiologic Variables with 70% Nitrous Oxide Added to Ketamine

	Postinduction time							
	30 min	31 min*	35 min*	40 min*	45 min*	50 min	55 min	60 min
MBP (mmHg)	109 ± 10	107 ± 9	107 ± 8	104 ± 13	104 ± 10	102 ± 12	100 ± 11	102 ± 12
HR (b/min)	94 ± 18	90 ± 15	85 ± 16	81 ± 18†	80 ± 15†	89 ± 18	88 ± 18	86 ± 16
T (°C)	36.4 ± 0.5	36.4 ± 0.5	35.4 ± 0.4	36.3 ± 0.5	36.3 ± 0.5	36.2 ± 0.4	36.2 ± 0.5	36 ± 0.5
ET_{CO_2} (mmHg)	30 ± 2	32 ± 2	32 ± 2	31 ± 2	30 ± 2	28 ± 2	30 ± 2	30 ± 2
ET_{N_2O} (mmHg)	—	58.9 ± 7.6	65.2 ± 2.6	66.4 ± 0.7	67.3 ± 0.4	11.6 ± 2.6	8.7 ± 2.1	2.4 ± 0.6

* Nitrous oxide added.

† $P < 0.01$ *vs.* 30 min.

TABLE 3. Evoked Potential Amplitude (mV) After Ketamine (Mean ± SD)

	Postinduction Time						
	Pre	2 min	5 min	10 min	15 min	20 min	30 min
Erbs	2.55 ± 1.26	2.26 ± 1.21	2.28 ± 1.13	2.25 ± 1.14	2.10 ± 0.94	2.07 ± 0.89	2.03 ± 0.89
Clls	2.41 ± 0.87	2.21 ± 0.96	2.21 ± 0.94	2.28 ± 0.86	2.21 ± 0.90	2.25 ± 0.85	2.20 ± 0.88
N1-P1	2.58 ± 1.05	2.97 ± 1.39*	2.98 ± 1.20*	2.90 ± 1.22†	2.75 ± 1.09	2.76 ± 1.12	2.74 ± 1.11
P1-N2	2.12 ± 1.50	3.84 ± 2.08*	3.99 ± 1.76*	3.72 ± 1.62*	3.48 ± 1.65*	3.39 ± 1.64*	3.32 ± 1.52*

* $P < 0.01$ *vs.* PRE.

† $P < 0.05$ *vs.* PRE.

and from 6–68% at 30 min postinduction. Mean P1-N2 amplitude increased significantly ($P < 0.01$) over PRE at all times after ketamine. Individual P1-N2 amplitude measurements increased in all patients 5 min after, and in 15/16 patients, 30 min after induction with ketamine. The amplitude enhancement was quite variable, ranging from 6–493% at 5 min, and from 18–293% at 30 min. An example of cortical waveforms recorded before and after ketamine appears in figure 1. The ratios of cortical amplitude at 5, 10, and 30 min postinduction and cortical amplitude at PRE were similar among patients who received labetolol for control of hypertension when compared to those who did not receive labetolol.

Figure 2 illustrates the effect of N_2O on cortical SSEP waveform during the ketamine anesthetic. Nitrous oxide resulted in an immediate and consistent reduction in N1-P1 and P1-N1 amplitude. The ketamine-enhanced mean cortical P1-N2 amplitude decreased by approximately 50% with the addition of N_2O. However, even this depressed level still represents approximately 63–86% of preinduction baseline amplitude (fig. 3). Once N_2O was discontinued, cortical SSEP amplitude recovered to within 85–90% of its pre-N_2O baseline.

Discussion

Our data indicate that ketamine, when used as a general anesthetic, significantly enhances the cortical amplitude of human median nerve SSEPs. Higher cortical amplitudes were seen for as long as 30 min after induction with ketamine. However, when N_2O was later added to the anesthetic regimen, ketamine was ineffective at preventing the known cortical SCEP amplitude depressant action of N_2O.[4] Nevertheless, cortical amplitude appeared to be maintained at a higher level with the combination of ketamine and N_2O than would be expected with N_2O alone, indicating that the ketamine-enhancing effect may persist even after N_2O. The fact that cortical amplitude returned to above preinduction baseline levels after discontinuance of N_2O suggests that the effect of ketamine may persist as long as 1 h with the regimen employed. Although we did not compare the effect of ketamine to that of other anesthetics, our results suggest that the effect of ketamine on SCEPs is markedly less depressant than that observed with certain other anesthetics, such as barbiturates,[5–7] potent halogenated agents,[8] or even opioids.[9,10] At anesthetic doses, these agents have been reported to depress amplitude by as much as 50% and can prolong latency significantly.

The effect of ketamine on human SSEPs has not been well documented previously. Ketamine was anecdotally noted to provide satisfactory recording conditions for lower extremity SSEPs in patients undergoing scoliosis surgery.§ Suzuki[11] mentions that ketamine depresses SSEPs but provides no further details. In a study comparing the neurophysiologic effects of different pain treatment modalities in awake human volunteers, Saletu *et al.*[12] reported a highly significant decrease in the amplitude of the "primary response" (corresponds to our N1-P1 amplitude) after intramuscular ketamine. Saletu's work is difficult to interpret because patients in the ketamine group received doses ranging from 1–5 mg/kg im and experienced a variety of side effects (restlessness, irritability, tremor) that could have engendered noise artefacts, possibly reducing evoked potential amplitude. Furthermore, a considerable number of subjects received

TABLE 4. Evoked Potential Amplitude with 70% N_2O Added to Ketamine (Mean ± SD)

	Postinduction Time							
	30 min	31 min*	35 min*	40 min*	45 min*	50 min	55 min	60 min
Erbs	2.03 ± 0.89	1.98 ± 0.94	2.09 ± 0.87	2.17 ± 0.90	2.10 ± 0.9	2.30 ± 1.14	2.46 ± 1.2	2.47 ± 1.36
Clls	2.20 ± 0.88	1.98 ± 0.80	2.17 ± 0.79	2.15 ± 0.73	2.21 ± 0.7	2.40 ± 0.82	2.36 ± 0.88	2.37 ± 0.85
N1-P1	2.74 ± 1.11	1.64 ± 0.63†	1.55 ± 0.61†	1.47 ± 0.63†	1.35 ± 0.52†	2.28 ± 0.87	2.42 ± 0.9	2.35 ± 0.89
P1-N2	3.32 ± 1.52	1.84 ± 0.87†	1.71 ± 0.66†	1.73 ± 0.77†	1.72 ± 0.71†	2.97 ± 1.35	2.96 ± 1.30	2.97 ± 1.52

* Nitrous oxide added.

† $P < 0.01$ *vs.* 30 min and $P < 0.05$ *vs.* 50–60 min.

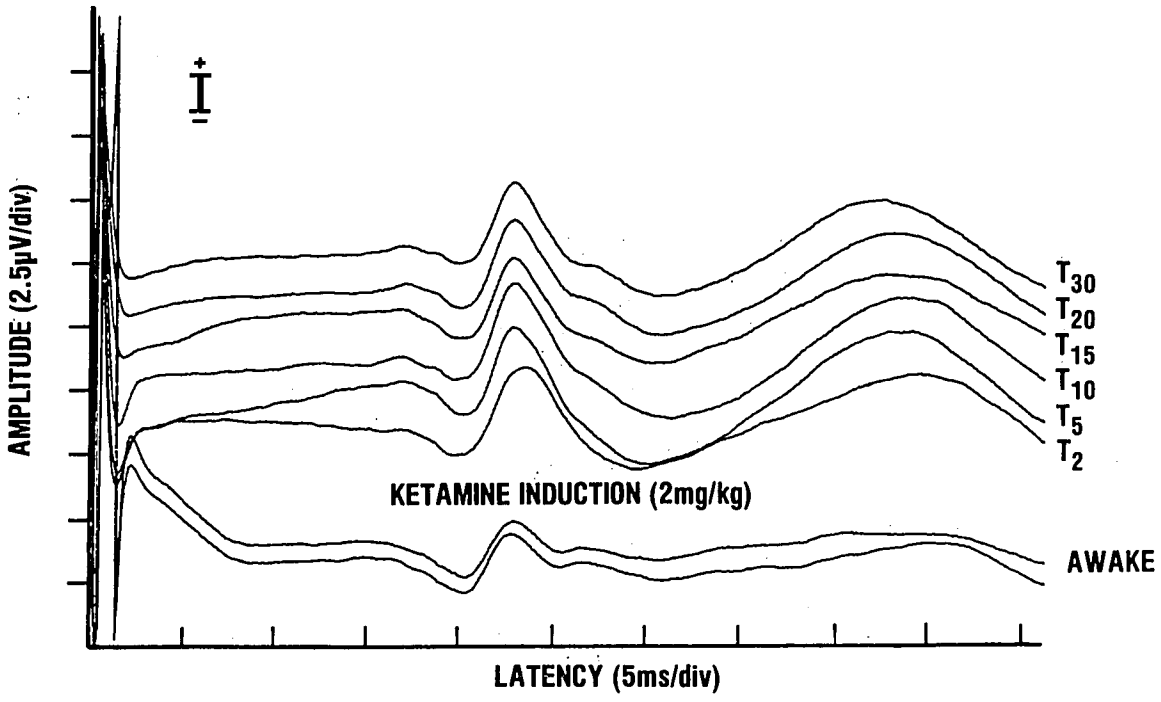

FIG. 1. Example of SCEP wave forms before and after induction with ketamine.

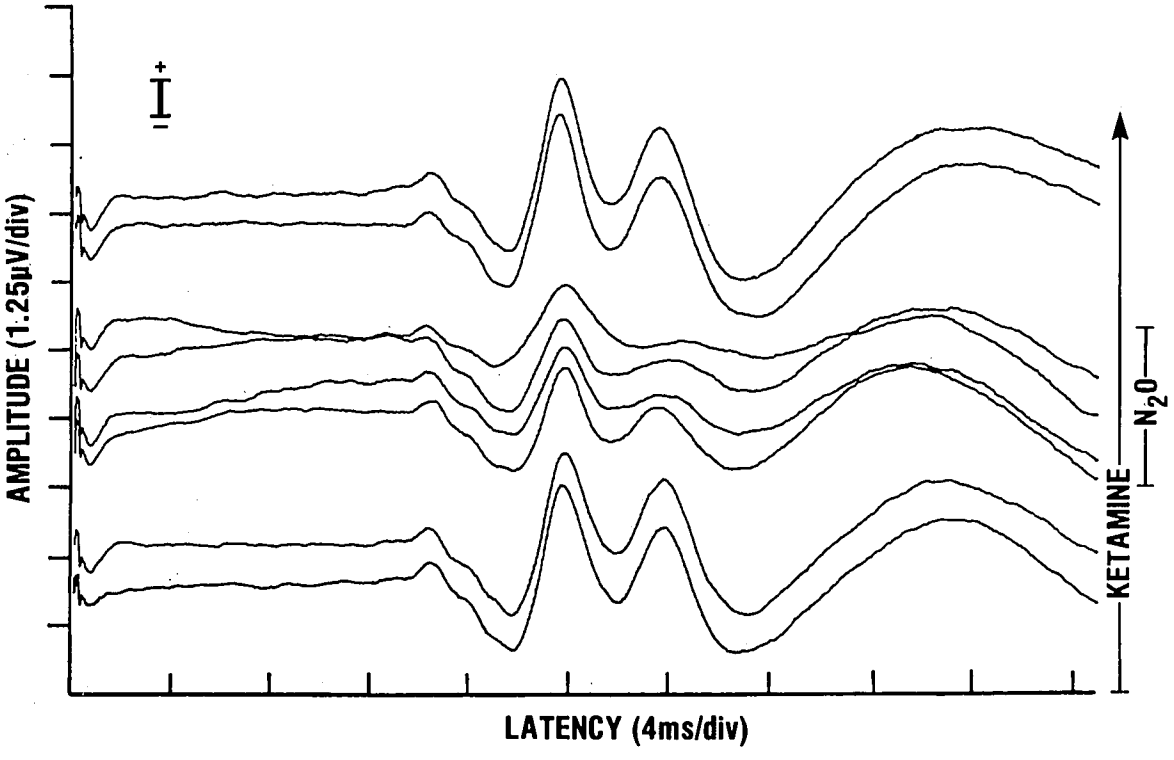

FIG. 2. Illustration of the effect of N_2O on SCEP wave forms when added to a ketamine background anesthetic.

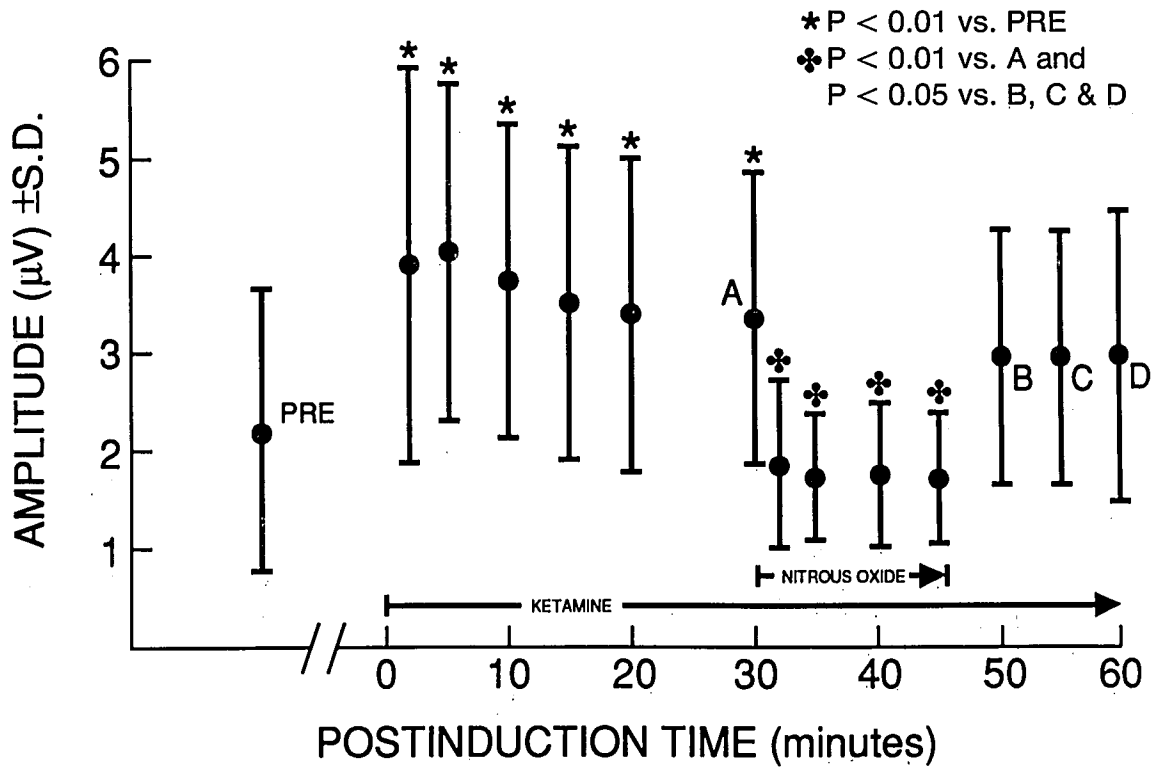

FIG. 3. P1-N2 amplitude (mean ± SD) with ketamine and ketamine/N_2O. A, B, C, D represent P1-N2 amplitude before and 5, 10, and 15 min after nitrous oxide.

diazepam im for ketamine related side effects. Diazepam has been reported to depress SCEPs.[13,14]

Available animal data show the effects of ketamine on the SCEP to be variable. Rat SCEP amplitude diminished with ketamine administration while latency increased.[15] Yet low doses of ketamine (up to 3 mg/kg iv) appeared to leave feline median nerve SCEPs unaffected, while higher doses significantly depressed SCEP amplitude.[5] Working with primates, Sparks *et al.*[16] showed that ketamine increased the amplitude of single shock potentials recorded in the association somesthetic cortex after thalamic stimulation. The effect of ketamine on other intermediate latency cortical evoked responses such as the auditory middle latency response (MLR) and the visual evoked potential (VEP) has also been reported. Dafny and Rigor[17] showed consistent enhancement of MLR amplitude with anesthetic doses of ketamine (80 mg/kg ip) in rats. In guinea pigs both enhancement and depression of MLR amplitude has been observed with large doses of ketamine (100 mg/kg ip or im).[18,19] By contrast, ketamine appeared not to affect VEPs in primates[20] or enhanced them in other species.[21,22] Also, ketamine made the VEP more prominent[22] when compared to the effect of barbiturates. When considering the results of these studies, it should be pointed out that many variables known to affect evoked potentials, such as P_{CO_2}, P_{O_2}, temperature and state of neuromuscular activity, were often either not reported or not rigorously controlled, making comparison with our results difficult. However, we believe that our human data support prior observations noting a stimulatory effect of ketamine on cortical components of the sensory evoked response.

Few other anesthetics have been reported to enhance evoked potentials. Etomidate produces very large SCEP waveform components corresponding to our N1, P1, and N2 deflections and also reduces the number of observable peaks.[1,23,24] Propofol,[2] meperidine, and low-dose thiopental[25] have also been reported to enhance early SCEP components at least transiently, although in some instances a reduction of spontaneous neuromuscular activity could have accounted for the observed effect. Augmentation of SCEP amplitude has been reported with enflurane[26] but other work has failed to support this finding.[8] Anesthetic agents reported to enhance SCEP amplitude leave subthalamic SSEP waveforms largely unaffected. Our work with ketamine shows a similar pattern. Ketamine did not affect the amplitude of the peripheral nerve (Erbs) or the spinal cord (Clls) potentials, but progressively enhanced the amplitude measured between waveform peaks thought to originate at and rostral to the thalamic area. The P1-N2 amplitude (P1 and N2 are felt to represent cortical generators) was most prominently

affected, suggesting that ketamine's effect on the SSEP may be mediated at the level of the somatosensory cortex. An alternate explanation requires postulating lysis of tonic inhibitory cortical or subcortical activity by ketamine.

Explanations for the observed enhancement of SCEP amplitude in the present study remain speculative. Elimination of muscular artefact due to pharmacologically induced neuromuscular blockade is known to improve evoked potential waveforms.[3] Yet our preinduction recordings were of very good quality as evidenced by a cortical noise amplitude ratio > 4.[3] There was no significant improvement in the noise amplitude ratio postinduction, which renders the possibility that the observed amplitude enhancement was due to the effects of neuromuscular blockade less likely. It also is conceivable that the administration of labetolol to some patients could have affected our results. However, the cortical amplitude to baseline amplitude ratios in those patients who required labetolol were generally not different from those who did not. Furthermore, there was no consistently positive correlation between the magnitude of the cortical amplitude ratio and the level of MAP or HR at 2, 5, or 10 min postinduction. This argues against hemodynamic changes affecting our electrophysiologic results. Surgical stimulation can transiently enhance SCEP¶ amplitude and may have resulted in underestimating the effect of N_2O in our study since N_2O was added with incision. It has been suggested that SSEP latency and amplitude changes might reflect depth of anesthesia rather than the influence of the specific anesthetic.[27] Our data are not in agreement with this viewpoint as they add to the available evidence that certain anesthetics affect evoked neural activity very differently than others. It is still conceivable, however, that dose and anesthetic depth-related effects may be seen within the pattern of the evoked potential changes characteristic of a particular anesthetic agent.

Our observations in the present study are of interest in terms of their implications for intraoperative monitoring of SEPs. While ketamine can lead to acute intracranial hypertension in susceptible patients and is therefore rarely suitable as the sole anesthetic for patients with reduced intracranial compliance, combinations of ketamine with other anesthetics could be advantageous in certain situations.[28,29] Considering the known bronchodilatory and hemodynamically stimulating properties of ketamine, it is conceivable that this agent may be employed even in patients with neurologic injury for specific indications. Ketamine might therefore be used as part of an anesthetic in acute trauma (excluding head injury) complicated by hemodynamic instability or bronchospasm. If spinal cord function needs to be monitored in this situation (*e.g.*, during spine or aortic surgery), knowledge of the effects of ketamine on the SCEP may provide useful information to the monitoring team. In this context, one should remember that magnitude of the enhancement of SCEP amplitude by ketamine was extremely variable. Nevertheless, in some situations ketamine could prove useful to enhance SCEPs that are otherwise too poor to be monitored intraoperatively. Such a situation has recently been reported with etomidate.[30] Further studies of anesthetic regimens incorporating ketamine will be needed to investigate whether this agent can counteract the tendency of other anesthetics to depress the SCEP and therefore can facilitate intraoperative monitoring.

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