

Effects of Propofol, Sevoflurane, Remifentanyl, and (S)-Ketamine in Subanesthetic Concentrations on Visceral and Somatosensory Pain-evoked Potentials

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ABSTRACT

Background: Although electroencephalographic parameters and auditory evoked potentials (AEP) reflect the hypnotic component of anesthesia, there is currently no specific and mechanism-based monitoring tool for anesthesia-induced blockade of nociceptive inputs. The aim of this study was to assess visceral pain-evoked potentials (VPEP) and contact heat-evoked potentials (CHEP) as electroencephalographic indicators of drug-induced changes of visceral and somatosensory pain. Additionally, AEP and electroencephalographic permutation entropy were used to evaluate sedative components of the applied drugs.

Methods: In a study enrolling 60 volunteers, VPEP, CHEP (amplitude N2-P1), and AEP (latency Nb, amplitude Pa-Nb) were recorded without drug application and at two subanesthetic concentration levels of propofol, sevoflurane, remifentanyl, or (s)-ketamine. Drug-induced changes of evoked potentials were analyzed. VPEP were generated by electric stimuli using bipolar electrodes positioned in the distal esophagus. For CHEP, heat pulses were given to the medial aspect of the right forearm using a CHEP stimulator. In addition to AEP, electroencephalographic permutation entropy was used to indicate level of sedation.

Results: With increasing concentrations of propofol, sevoflurane, remifentanyl, and (s)-ketamine, VPEP and CHEP

What We Already Know about This Topic

- Analgesia during general anesthesia is difficult to assess using available monitors
- Sensory-evoked electroencephalographic potential monitoring provides a possible monitor of intraoperative analgesia

What This Article Tells Us That Is New

- In human volunteers, subanesthetic doses of propofol, sevoflurane, remifentanyl, and (s)-ketamine had suppressive effects on both visceral and somatic pain-evoked potentials, even though the electroencephalographic parameters did not show effects of sedation
- Pain-evoked potential monitoring indicates antinociceptive effects of anesthetic drugs and suggests possible use as an intraoperative measure of analgesic effects

N2-P1 amplitudes decreased. AEP and electroencephalographic permutation entropy showed neither clinically relevant nor statistically significant suppression of cortical activity during drug application.

Conclusions: Decreasing VPEP and CHEP amplitudes under subanesthetic concentrations of propofol, sevoflurane, remifentanyl, and (s)-ketamine indicate suppressive drug effects. These effects seem to be specific for analgesia.

THE main components of general anesthesia include loss of consciousness, amnesia, immobility, and analgesia.¹ Although monitoring of neuromuscular blockade and the hypnotic component of anesthesia has recently gained popularity in daily clinical practice, there is currently no specific monitor of analgesia. To date, levels of the analgesic component of anesthesia are estimated by surrogate parameters such as heart rate, blood pressure, and drug concentrations. It is assumed that a reaction of the cardiovascular system during adequate hypnosis reflects perception of pain. The relevance of an earlier detection of inadequate analgesia as well as the possibility to evaluate intraoperative pain more objectively is evident.

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Evoked potentials are derived from the electroencephalogram in response to various sensory stimuli and reflect the functional integrity and reactions of neuronal pathways of the peripheral and central nervous systems. Changes of evoked potentials allow the assessment of anesthetic drug effects, with the nervous system as their main target. It has been shown that latencies of mid-latency auditory evoked potentials (MLAEP) quantify the hypnotic component of anesthesia.^{2,3} The Nb peak of the MLAEP wave has been recommended as a good discriminator of being awake and anesthetized, as its latencies increase and amplitudes decrease with deeper levels of anesthesia.^{2,4,5} In addition to evoked responses, electroencephalogram parameters and indices can be used to assess the level of anesthesia.⁶ The recently introduced permutation entropy (PeEn) of the electroencephalogram reflects nonlinear dynamics of brain activity and changes with depth of anesthesia.^{7,8} Amplitudes of pain-evoked potentials have been suggested to assess the intensity of pain.^{9–12} Pain itself can be separated according to its characteristics, that is, visceral and somatic pain, which must be regarded separately.^{13,14} Although imaging studies show similarities in the activated cortical network by visceral and somatic pain,^{15,16} differences in the central processing structures and the peripheral pain-conducting fibers are well known between both pain modalities.¹⁷ Contact heat evoked-pain is mainly conducted by A δ -fibers,^{18–23} whereas a concomitant involvement of C-fibers²¹ is disputed.²³ In visceral pain, both A δ -fibers and C-fibers are involved,^{24–28} and the painful component is particularly conducted by C-fibers, in contrast to nonpainful visceral stimuli.^{27,29}

The relevance of these different fiber structures is obvious as antinociception of different analgesics can be caused by interaction with A δ - or C-fibers.^{30–39}

The primary aim of this study was to detect drug-induced changes of visceral pain-evoked potentials (VPEP) and contact heat-evoked potentials (CHEP) because they may be used as indicators of antinociceptive effects on visceral and somatosensory pain. Therefore, drug effects on VPEP and CHEP N2-P1 amplitudes, reflecting visceral and somatic pain intensity,^{29,40} were analyzed. The secondary aim of the study was to evaluate whether observed changes may also be due to sedative effects of the administered drugs. For this purpose, MLAEP^{2,3} and PeEn^{7,8} of the electroencephalogram, which indicate the sedative component of anesthesia, were measured, because concomitant changes in MLAEP or PeEn during propofol, sevoflurane, remifentanyl, and (s)-ketamine administration may indicate that changes of pain evoked potentials are unspecific.

Materials and Methods

Protocol Design and Data Collection

The study was performed in 60 healthy male volunteers (American Society of Anesthesiologists physical status 1). After approval from the Ethics Committee of the Klinikum rechts der Isar, Munich, Germany, informed written consent was obtained from all volunteers. All subjects underwent

a medical interview. Exclusion criteria were a history of cardiovascular, gastrointestinal, or neurological disease; hearing impairment; any chronic pain; or a history of substance abuse. Participants were not allowed any oral intake for 6 h before drug administration. A total of 15 subjects were assigned in a randomized order to one of the four different drugs propofol, sevoflurane, remifentanyl, and (s)-ketamine. Participants were paid for attendance.

One study-day was appointed per subject, as the test lasted for approximately 8 h including preparation and post-processing. In order to familiarize the volunteers with the procedure, all experiments were explained before trial testing was performed. Standard monitoring parameters such as electrocardiogram, blood pressure, pulse, and oxygen saturation were recorded continuously with a Datex AS/3 monitor (Datex-Ohmeda Division Instrumentation Corp., Helsinki, Finland). An indwelling intravenous catheter was placed to infuse the drug to be tested and an infusion with Ringer's acetate. Each subject received oxygen *via* a nose probe during the trial. The study was conducted in a quiet, semi-darkened room and controlled by video surveillance from a separate room.

Intravenous drug administration was performed by a target-controlled infusion pump (target-controlled infusion, space-infusion pump, B. Braun Medical, Melsungen, Germany) to reach and maintain constant target plasma concentrations. Sevoflurane was delivered *via* face mask (breathing system Dräger Sulla 808V, Dräger Medical Deutschland GmbH, Lübeck, Germany). All drugs were given in subanesthetic doses to specify antinociceptive and sedative components. Subanesthetic concentrations contained the following three concentration levels, which were selected to maintain consciousness: at level I, no drug was applied; at level II, propofol effect site concentration was 0.50 $\mu\text{g/ml}$, target concentration of sevoflurane was 0.40 vol%, continuous infusion rate of remifentanyl was 0.05 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and that of (s)-ketamine was 0.25 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. At level III, propofol was applied at 1.00 $\mu\text{g/ml}$, sevoflurane at 0.80 vol%, remifentanyl at 0.15 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and (s)-ketamine at 0.50 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. Tests were performed after 15 min of equilibration at a constant concentration. At each of the three drug levels, auditory evoked potentials (AEP), VPEP, and CHEP were recorded successively. The study design is shown in figure 1.

The electroencephalogram was recorded from 32 surface electrodes using a standard electroencephalogram cap (EASYCAP, Brain Products, Gilching, Germany) according to the international 10–20 system. Impedances were kept below 5 kOhm. Multichannel electroencephalogram (29 channels), electrocardiogram (2 channels), and electrooculogram (1 channel) were recorded continuously at a sampling rate of 5 kHz using BrainAmp (Brain Products GmbH) electroencephalographic amplifier and BrainVision Recorder (Brain Products GmbH) data-acquisition software. The subjects were instructed to close their eyes and lie quiescently during measurements to reduce artifacts, for example, eye

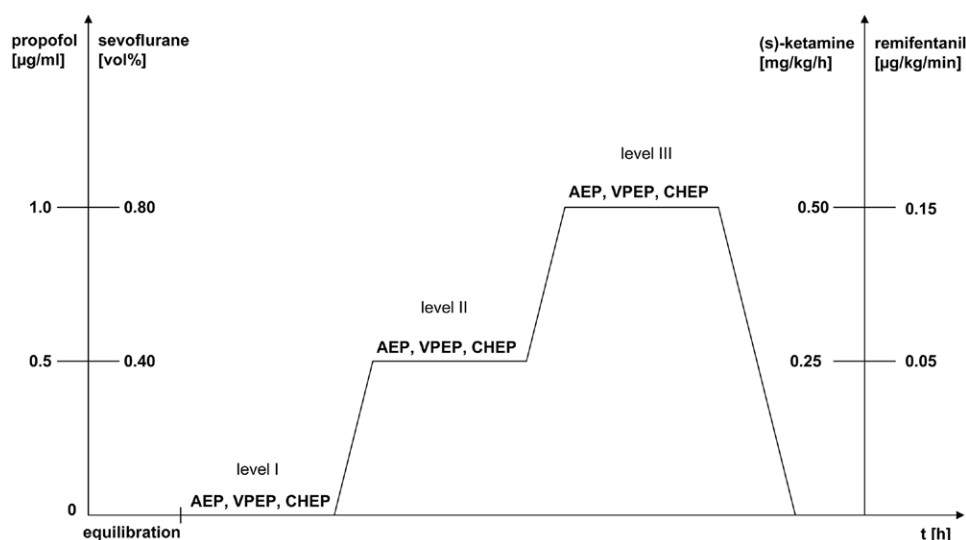


Fig. 1. Design of the study. AEP, VPEP, and CHEP were recorded successively at level I without drug application (baseline) after equilibration; at level II under either propofol (0.5 $\mu\text{g/ml}$), sevoflurane (0.40 vol%), (s)-ketamine (0.25 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$), or remifentanyl (0.05 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$); and at level III under higher concentrations of either propofol (1.0 $\mu\text{g/ml}$), sevoflurane (0.80 vol%), (s)-ketamine (0.50 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$), or remifentanyl (0.15 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). AEP = auditory evoked potential; CHEP = contact heat-evoked potential; VPEP = visceral pain-evoked potential.

movements and muscle activity. An electro stimulator (Konstantstrom Stimulator, Lucius & Baer GmbH, Geretsried, Germany) was used to generate VPEP and a computerized thermal contact stimulator (CHEPS[®], Medoc Ltd., Ramat Yishai, Israel) controlled by CHEPS[®] software 2.2 (Medoc Ltd.) for CHEP. Triggers for AEP, VPEP, and CHEP were generated as transistor–transistor logic onset impulse and recorded by a further personal computer. Synchronous to electroencephalogram, AEP, VPEP, and CHEP data acquisition; standard anesthesia monitoring data; storage of events; and standardized comments such as data of the target-controlled infusion pump were recorded simultaneously using the software NeuMonD (Department of Anesthesiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany).⁴¹

Evoked Potentials

Auditory evoked potentials were calculated from electroencephalographic channel TP9 (reference Fcz) using an auditory stimulus (binaural clicks) of 70 dB above hearing threshold with a repetition rate of 8.3 Hz ($\pm 10\%$ interstimulus variability). Electroencephalographic data and AEP processing with BrainVision Analyzer 1.05 (Brain Products GmbH) software include the following steps: (1) bandpass zero phase butterworth filtering from 26 to 400 Hz, (2) down sampling at 1 kHz, (3) exclusion of electroencephalogram signals with amplitudes below 0.5 μV and above 200 μV within a timespan of 500 ms pre- and 500 ms poststimulus, and (4) averaging of one AEP signal for each drug level and each subject using 4,000 sweeps of 130 ms length starting 10 ms before stimulus (average all). After visual inspection, local positive and negative peaks (minimum and maximum) were identified

and AEP wave Nb was analyzed with respect to latency as an indicator of the hypnotic component of anesthesia.^{2,3} AEP Pa-Nb peak-to-peak amplitudes were analyzed to test drug-induced suppression of cortical activity in general.

VPEP stimulation was performed *via* a bipolar electrode developed by the authors. The catheter was passed transnasally and positioned in the distal esophagus. The individual pain threshold was determined in 0.1 mA steps in ascending order and identified as soon as the volunteer reported a diffuse heartburn in the area of the lower one-third of the sternum. Then the electrode position was fixed in contact to the esophagus wall *via* vacuum. Four iterations of 50 electric stimuli (rectangular pulse) above pain threshold were applied per run at a stimulus rate of 0.125 Hz.

For VPEP processing, electroencephalogram data were filtered (0.5–12 Hz digital zero phase butterworth bandpass filter) and down-sampled at 156 Hz. Signals with amplitudes greater than 100 μV were rejected.²⁴ Average of all analysis included 200 sweeps of 2-s length (from 1 s pre- to 1 s poststimulus) per level for each subject (electrode positions TP9-Fcz). The peaks P1 and N2 were identified and peak-to-peak amplitudes were analyzed (N2-P1).

With a combination of a heating foil and a Peltier element for active back-cooling, the CHEPS[®] device generates rapid temperature changes. The thermofoil permits a heating rate of 70°C/s from a nominal baseline temperature of 32°C up to a maximum temperature of 55°C. Pain modality is a strong, sharp heat pain. The stimulator probe was manually held, and to avoid erythemas or receptor fatigue, the thermode was moved slightly between five stimuli while care was taken to keep good contact between the probe and the subject's skin. Heat pulses were given to the medial aspect

of the right forearm. One stimulus block consisted of 5×40 stimuli with an interstimulus variability of $8 \text{ s} \pm 10\%$ and an intrastimulus variability of $1 \text{ s} \pm 10\%$. A total of 200 stimuli were given above the pain threshold, which was determined before the recordings by increasing the CHEPS[®] temperature stepwise until the subject reported pain.

After digital zero phase bandpass filtering (0.3–30 Hz), CHEP were averaged using sweeps of 2,048 ms (1 s pre- and 1,048 ms poststimulus).⁴² Only signals with amplitudes between -100 and $100 \mu\text{V}$ were included. After averaging (200 sweeps per level for each subject, TP9-Fcz) CHEP, peaks P1 and N2 were identified and N2-P1 amplitudes were analyzed.

All peaks were visually identified by three independent experts. Amplitudes of VPEP and CHEP were put to “0” in terms of a maximum suppression effect at level II or III, if they did not increase apart from the background noise, but were identifiable at level I (baseline).

Permutation Entropy

Artifact-free electroencephalogram sequences with and without stimulation were selected at each level of drug concentration. PeEn was calculated from all 29 channels of electroencephalogram data (10 s signal length, 0.5–30 Hz bandwidth, 200 Hz sampling frequency, and an embedding dimension of 5).

Signal Analysis and Statistical Analysis

The Wilcoxon signed-rank test was used to analyze changes of VPEP and CHEP amplitudes between concentration levels I and II and level I and III. In order to adjust *P* values for multiplicity, the Dunnett correction method was used. Values of AEP latencies and amplitudes and of PeEn (29 electrodes, clustered) at levels I, II, and III are illustrated in box plots. Additionally, a Wilcoxon test was performed to indicate changes of AEP and PeEn (Dunnett correction for multiple comparisons). Statistical tests were conducted two-sided, and an adjusted *P* value less than 0.05 was considered to indicate statistical significance. Signal processing and statistical analysis were performed using BrainVision Analyzer 1.05, LabVIEW 6.0 (National Instruments, Austin, TX), and R 2.4.0 (R Foundation for Statistical Computing, Vienna, Austria) on personal computers with Windows XP (Microsoft Corporation, Redmond, WA).

Results

Demographic data were similar in all the four groups (propofol, sevoflurane, remifentanyl, (s)-ketamine), as shown in table 1.

In the propofol and remifentanyl groups, all participants completed the experiment. One of the 15 subjects who received (s)-ketamine did not tolerate the concentrations at level III, and the protocol was stopped for this subject after completed measurements at level II. Four of the subjects who received sevoflurane were psychomotorically profoundly agitated under 0.8 vol% sevoflurane and the experiments were stopped because of subsequent artifacts in the electroencephalogram (after completed measurements at level II). No relevant cardiovascular or respiratory side effects were seen during the study. Signs of sedation were observed in some subjects, but never reached a level of deep sedation.

The mean pain threshold for electric stimulation in the esophagus was $36.2 \pm 9.6 \text{ mA}$ (range 15.4–65.6 mA), with slight differences between groups (propofol group: $40.1 \pm 12.7 \text{ mA}$; sevoflurane group: $35.2 \pm 7.6 \text{ mA}$; remifentanyl group: $34.7 \pm 9.2 \text{ mA}$; and (s)-ketamine group: $34.8 \pm 8.3 \text{ mA}$). The mean pain threshold for contact heat stimuli was $53.3 \pm 1.9^\circ\text{C}$ (range 45° – 55°C), without differences between the four groups (propofol group: $53.1 \pm 2.8^\circ\text{C}$; sevoflurane group: $53.7 \pm 1.6^\circ\text{C}$; remifentanyl group $53 \pm 1.7^\circ\text{C}$; and (s)-ketamine group $53.3 \pm 1.4^\circ\text{C}$).

Examples of VPEP and CHEP are illustrated in figure 2. Results of VPEP and CHEP N2-P1 amplitudes are shown in table 2. VPEP N2-P1 amplitudes decreased significantly between level I and II (D1) and level I and III (D2) for propofol, remifentanyl, and (s)-ketamine. For sevoflurane, the decrease in VPEP amplitudes was not statistically significant. CHEP N2-P1 amplitudes also decreased with increasing concentrations of the four drugs, which was significant for propofol and remifentanyl between level I and level II, and between level I and III. For sevoflurane and (s)-ketamine, the decrease in CHEP amplitudes was not significant. Separated for each drug, figure 3 shows the effects on VPEP and CHEP amplitudes and interindividual variability.

According to figure 4, AEP and PeEn do not show significant suppression of cortical activity during drug application.

Discussion

In clinical routine, hemodynamic reactions to painful stimuli are used to assess the antinociceptive component of

Table 1. Demographic Data

Drug	No. of Subjects	Mean Age, yr	Mean Height, cm	Mean Weight, kg
Propofol	15	25 ± 3	182 ± 5	76 ± 7
Sevoflurane	15	26 ± 3	182 ± 8	84 ± 9
Remifentanyl	15	25 ± 2	182 ± 5	76 ± 8
(s)-ketamine	15	26 ± 3	181 ± 7	77 ± 8

Demographic data (means \pm SD) of the 60 volunteers subdivided toward the four drugs propofol, sevoflurane, remifentanyl, and (s)-ketamine. Differences were not significant, with exception of weight (Mann-Whitney U test, $P < 0.05$).

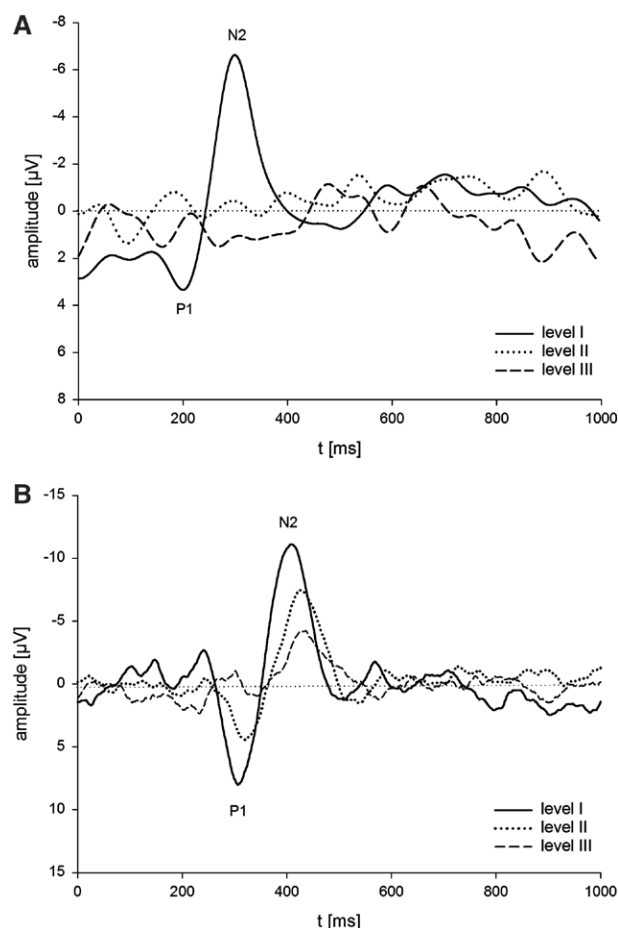


Fig. 2. Exemplary illustration of VPEP (A) and CHEP (B) at level I (lined), level II (dotted), and level III (dashed): decreasing P1-N2 amplitudes of VPEP and CHEP are shown under remifentanyl administration (average all data from a single volunteer for VPEP and CHEP). CHEP = contact heat-evoked potential; VPEP = visceral pain-evoked potential; I = baseline without any drug application; II = drug concentration level II (here: remifentanyl $0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$); III = drug concentration level III (here: remifentanyl $0.15 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$).

anesthesia. Unfortunately, blood pressure and heart rate are not specific and may not predict in advance, but only indicate insufficient analgesia, that is, they may show reactions to existing pain. Inadequate analgesia is related to intra- and postoperative complications, cardiovascular stress reactions, and changes at the cerebral network level.⁴³ Therefore, a specific and objective monitor of the analgesic component of anesthesia would add important information to standard anesthesia monitoring.

Before a specific monitor of the analgesic component can be developed, an appropriate definition of the measured effect is required. Pain is a complex sensation that includes both physiological and cognitive/emotional processes. Strictly speaking, the term antinociception refers to signal processing of noxious stimulus input which is independent of its conscious perception. In contrast, analgesia includes in addition the blockade of conscious pain perception and its

processing. The multiple and interdependent dimensions of pain are differentially affected by the different components and additive drug effects during general anesthesia. For example, sedation reduces the conscious perception of a painful stimulus, which by definition means “analgesia.” Still, this approach to analgesia may not be sufficient to block hemodynamic and neurohumoral changes to painful stimuli or prevent pain-related adverse reactions.

Electroencephalographic Measurements to Evaluate Effects of Subanesthetic Drug Concentrations

The current study focused on pain-evoked potentials and their reactions to drugs as a first step to investigate feasibility of these signals as an objective and direct measure of antinociceptive drug effects. Pain-evoked potentials capture the reaction of cerebral activity to a painful stimulus and may, therefore, be suitable to monitor specific effects on the main target organ. Secondary, it was explored whether sedative drug effects may be the reason for changes of pain-evoked potentials. Therefore, analysis of AEP latencies and amplitudes and of electroencephalographic PeEn is used according to the present literature.^{2–5,7,8}

Subanesthetic concentrations of the four drugs induced conscious sedation, during which the subjects responded to verbal commands and both cardiovascular and respiratory functions were maintained. The four drugs all show analgesic or hypnotic effects to different degrees. Whereas anesthetics such as sevoflurane and propofol may also induce analgesia by reduction of conscious processing of pain, analgesics such as remifentanyl may also show sedative effects. Subanesthetic concentrations allow a differentiation between preferentially hypnotic or analgesic effects.

Amplitudes of evoked potentials were shown to depend on stimulus intensity in the esophagus,^{12,24} gut,^{9,10} and at the skin.^{44,45} In particular, CHEP amplitudes are known to correlate with the individual intensity of heat pain.^{40,46} In this study, only drug concentrations were modified within a subanesthetic range, whereas stimulus intensity remained constant during the trial for both visceral and somatic pain. Therefore, a decrease in VPEP and CHEP amplitudes reflects drug-induced suppression of pain-related cerebral activity.

Habituation effects caused by repeated stimulation may also result in decreased amplitudes.⁴⁷ Still, the period of over 1 h between VPEP and respective CHEP recordings at levels I, II, and III is too long to maintain a potential habituation effect to repeated stimuli. Therefore, it is unlikely that decreasing VPEP and CHEP amplitudes are due to habituation effects to the stimulus.

In the current study, VPEP and CHEP are suppressed during drug application whereas AEP and PeEn showed no substantial changes. This may be due to different reasons.

Global Drug-induced Suppression of Cortical Activity

Generally, the decrease in VPEP and CHEP amplitudes may be due to a global suppression of cortical activity,

Table 2. Changes of Pain-evoked Potentials during Drug Application

	I	II	III	D1	D2
VPEP N2-P1 Amplitudes, μV					
Propofol	-7.4 ± 2.6 (n = 10)	-2.9 ± 3.2 (n = 10)	0 ± 0 (n = 9)	-4.5^* (P = 0.014)	-7.4^* (P = 0.016)
Sevoflurane	-5.9 ± 3.7 (n = 11)	-1.6 ± 2.1 (n = 7)	-0.3 ± 0.6 (n = 6)	-4.3 (P = 0.056)	-5.6 (P = 0.056)
Remifentanyl	-6.6 ± 1.8 (n = 8)	-0.6 ± 1.1 (n = 8)	-0.8 ± 1.9 (n = 7)	-6.0^* (P = 0.024)	-5.8^* (P = 0.036)
(s)-ketamine	-6.8 ± 4.3 (n = 9)	-3.6 ± 3.2 (n = 9)	-1.6 ± 1.3 (n = 7)	-3.2^* (P = 0.042)	5.2^* (P = 0.036)
CHEP N2-P1 Amplitudes, μV					
Propofol	-5.6 ± 2.7 (n = 8)	-2.4 ± 2.1 (n = 8)	-1.4 ± 1.8 (n = 7)	-3.2^* (P = 0.024)	-4.2^* (P = 0.036)
Sevoflurane	-5.0 ± 2.4 (n = 8)	-1.0 ± 1.5 (n = 5)	-0.9 ± 1.6 (n = 7)	-4.0 (P = 0.086)	-4.1 (P = 0.054)
Remifentanyl	-6.3 ± 5.6 (n = 8)	-3.3 ± 4.3 (n = 7)	-1.1 ± 2.0 (n = 7)	-3.0^* (P = 0.036)	-5.2^* (P = 0.036)
(s)-ketamine	-5.6 ± 1.9 (n = 6)	-3.9 ± 1.3 (n = 6)	-5.0 ± 1.6 (n = 5)	-1.7 (P = 0.232)	-0.6 (P = 0.690)

Values of VPEP and CHEP N2-P1 amplitudes (μV) for propofol, sevoflurane, remifentanyl, and (s)-ketamine (means \pm SD) for each drug concentration (level I, II, and III) including differences between drug level I and II (D1) and level I and III (D2) (* $P < 0.05$, Dunnett correction).

*Significant differences ($P < 0.05$, Dunnett correction).

CHEP = contact heat-evoked potential; D1 = differences between level I (baseline) and level II; D2 = differences between level I (baseline) and level III; I = baseline without any drug application; II = drug concentration level II (propofol: $0.5 \mu\text{g}/\text{ml}$, remifentanyl $0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, (s)-ketamine $0.25 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, and sevoflurane: $0.40 \text{ vol}\%$); III = drug concentration level III (propofol: $1.0 \mu\text{g}/\text{ml}$, remifentanyl $0.15 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, (s)-ketamine $0.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, and sevoflurane: $0.80 \text{ vol}\%$); VPEP = visceral pain-evoked potential.

as induced by sedation. If such a general suppression of evoked responses is suspected, it remains unclear why AEP are not suppressed. MLAEP Nb latencies can be used to assess the level of sedation. Increasing levels of sedation are reflected by increasing MLAEP latencies and decreasing amplitudes.^{2,4,5} The current results did not show changes of MLAEP latencies, whereas amplitudes even increased under propofol administration. These findings are in contrast to the hypothesis of a drug-induced suppression of cortical activity. Still, it cannot be excluded that MLAEP are not sensitive enough to detect minor drug effects, in particular, at the subanesthetic concentrations given. Furthermore, the auditory system may not be as sensitive to drug-associated effects as the pain system. Therefore, PeEn of the electroencephalogram was analyzed as a measure of the level of sedation.^{7,8} Analysis of PeEn also did not indicate a decrease in cortical activity. This supports the results obtained from MLAEP analysis. Therefore, it seems very unlikely that general suppression of cerebral activity due to sedative effects is the reason for decreasing amplitudes of pain-evoked potentials.

VPEP and CHEP Indicate Drug-specific Changes of Visceral and Somatosensory Pain

The presented results may also suggest that propofol, sevoflurane, remifentanyl, and (s)-ketamine all have analgesic

properties that are indicated by VPEP and CHEP. This would explain the decreasing amplitudes of pain-evoked potentials with concurrently unchanged AEP and PeEn. The decrease in VPEP and CHEP amplitudes is not homogeneous but depends on the applied drug and pain quality (visceral *versus* somatic). Although this may be due to variability only, results can easily be linked to the existing literature about specific analgesic effects of the four drugs. Both the analyzed VPEP and the CHEP peaks (P1 and N2) are the correlate of the exogenous, stimulus-dependent component of cortical activity.^{15,42} Therefore, differing decreases in VPEP and CHEP amplitudes may be associated with the different activated pain-conducting fibers. After noxious electrical stimuli of the viscera, both A δ - and C-fibers transmit the stimulus.^{25,26} Here, stimuli were applied at the pain threshold and therefore transmission *via* C-fibers is most likely.²⁷ If temperatures above 50°C are used to generate CHEP, the stimulus is mainly transmitted *via* A δ -fibers.^{18–21,23} In experimental settings, analgesic effects of propofol and sevoflurane have been demonstrated and it has been shown that they act differently on visceral and somatosensory pain.^{48–53} Antinociceptive effects of propofol have been shown for somatic pain in humans^{48,49} and recently for visceral pain in mice.⁵¹ For sevoflurane, there are clinical observations of analgesic effects during labor.^{52,53} Analgesic effects of subanesthetic remifentanyl concentrations have been shown in numerous studies,^{37,54} as well as effects

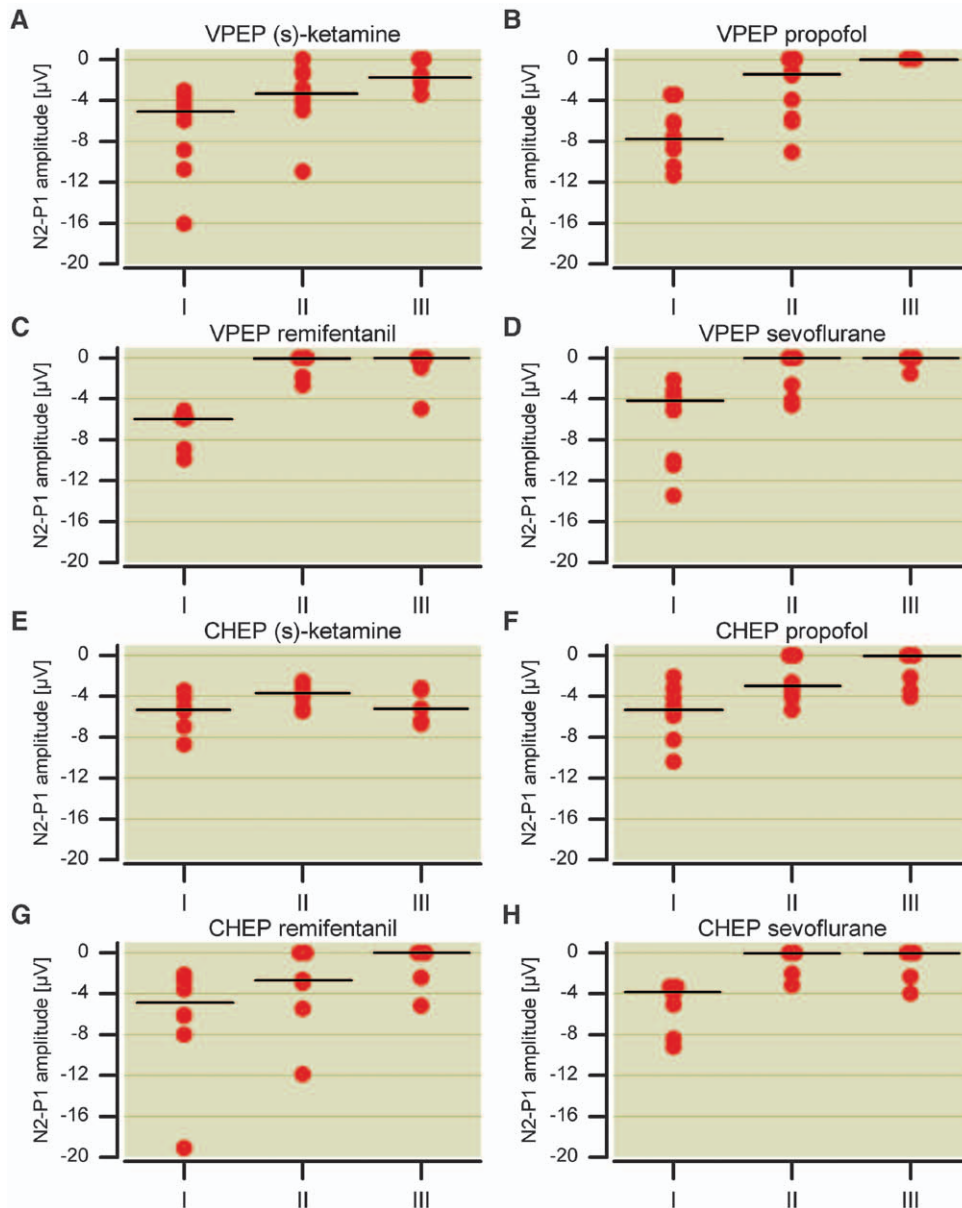


Fig. 3. Changes of VPEP and CHEP N2-P1 amplitudes. Interindividual values (dots) and median (crossbar) of VPEP (A–D) and CHEP (E–H) amplitudes are illustrated for level I, II, and III, separated for each drug. Suppressive drug effects are indicated by approximation of the negative potential to zero amplitude. CHEP = contact heat-evoked potential; VPEP = visceral pain-evoked potential; I = baseline without any drug application; II = drug concentration level II (propofol: 0.5 µg/ml, remifentanyl 0.05 µg·kg⁻¹·min⁻¹, (s)-ketamine 0.25 mg·kg⁻¹·h⁻¹, sevoflurane: 0.40 vol%); III = drug concentration level III (propofol: 1.0 µg/ml, remifentanyl 0.15 µg·kg⁻¹·min⁻¹, (s)-ketamine 0.5 mg·kg⁻¹·h⁻¹, and sevoflurane: 0.80 vol%).

on somatosensory evoked potentials.⁵⁵ However, opioids show a greater effect on visceral (C-fiber mediated) than on somatosensory pain (Aδ-fiber mediated).^{32–34,37} In imaging studies, analgesic effects of ketamine were observed without global cognitive effects under subanesthetic concentrations.⁵⁶ Surprisingly, in the current study, CHEP amplitudes increased with higher concentrations of (s)-ketamine compared to lower concentrations (level III *vs.* level II), although amplitudes were still lower compared with baseline (level III and II *vs.* level I). Lee *et al.*⁵⁷ recently showed unchanged heat pain threshold

but increased temporal summation threshold after CHEP stimulation, which was dose dependent with subanesthetic concentrations of ketamine. This result is hardly comparable with results obtained by evoked potentials. In particular, in this study, the early Aδ-fiber-mediated component of CHEP was analyzed, and not the ultra-late C-fiber-mediated component, which is related to wind-up. Thus, it remains unclear why we did not find a further decrease in CHEP amplitudes with higher concentrations of ketamine. The low number of available measurements may limit a detailed analysis.

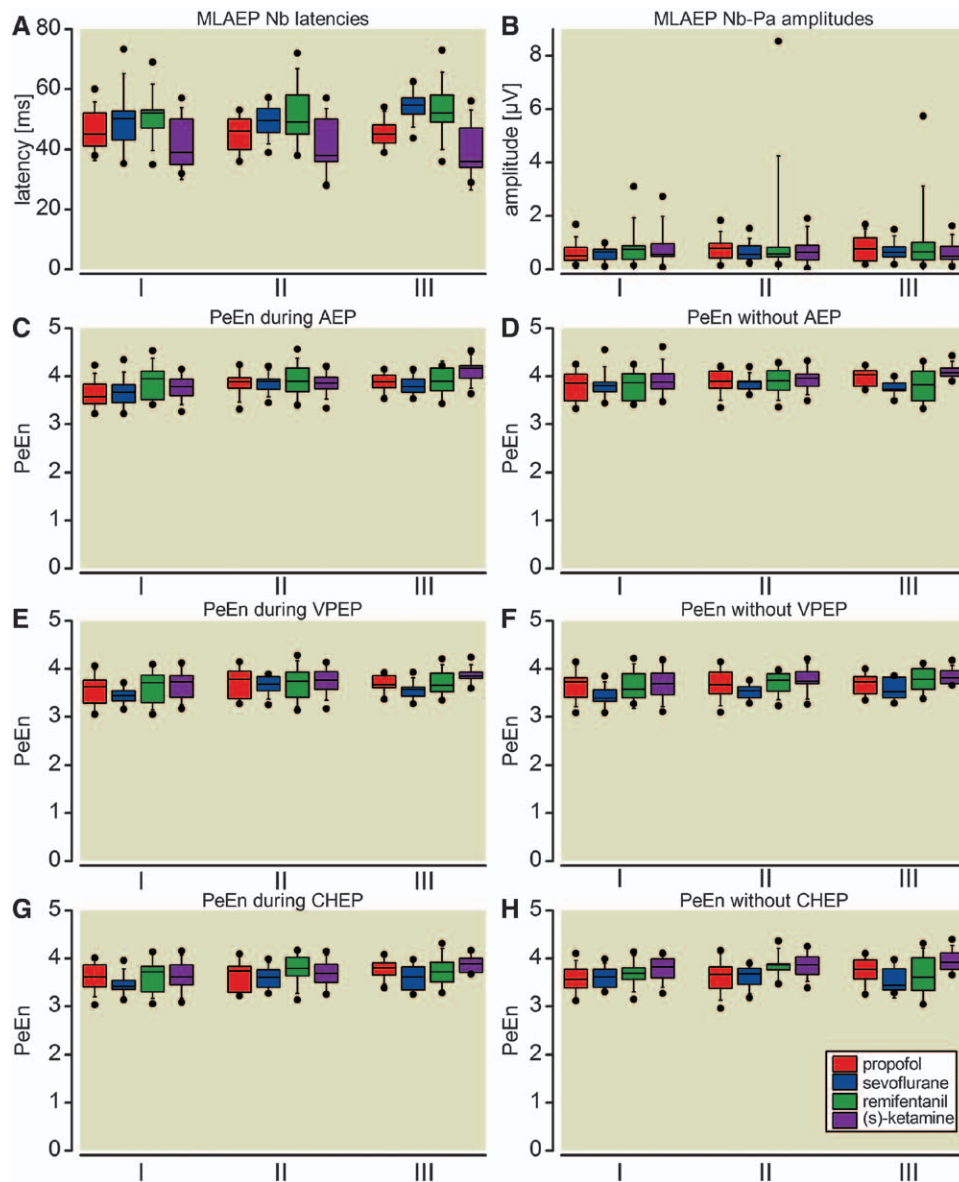


Fig. 4. Results of MLAEP Nb latencies (A) and Nb-Pa amplitudes (B) and of electroencephalographic PeEn during stimulation (C, E, G) and without stimulation (D, F, H). Boxplots are illustrated for each drug (in sequence of propofol [red], sevoflurane [blue], remifentanyl [green], and (s)-ketamine [purple]) and for each concentration level I–III. AEP = auditory evoked potential; CHEP = contact heat-evoked potential; MLAEP = mid-latency auditory evoked potential; PeEn = permutation entropy; VPEP = visceral pain-evoked potential; I = baseline without any drug application; II = drug concentration level II (propofol: 0.5 $\mu\text{g}/\text{ml}$, remifentanyl 0.05 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, (s)-ketamine 0.25 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, and sevoflurane: 0.40 vol%); III: drug concentration level III (propofol: 1.0 $\mu\text{g}/\text{ml}$, remifentanyl 0.15 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, (s)-ketamine 0.5 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, and sevoflurane: 0.80 vol%).

Finally, evoked potentials reflect summary effects on the central nervous system without giving detailed information about drug-specific sites of action and interaction. Cerebral mechanisms may be important for the obtained results because various dimensions of pain are influenced differently by each of the four drugs. For example, remifentanyl directly inhibits nociceptive information *via* opioid receptors located in the nervous system, whereas ketamine mainly acts on cerebral structures such as insula and anterior cingulate cortex and thereby modulates the emotional aspect of pain.⁵⁸

But such drug-specific interactions cannot be discussed solely on the basis of evoked potentials, and further studies are required.

Limitations

The current study has some limitations. First, only male subjects were investigated. Because of well-known, gender-specific differences related to pain,^{59,60} the current results cannot be generalized. In addition, there was no clinical assessment of drug effects on pain intensity or the level of

consciousness. In future studies, differential dose-dependent drug effects on evoked potentials should be correlated with detailed clinical scores to support the validity of VPEP and CHEP. Finally, the limited number of volunteers and a high dropout rate may limit the results of the current study. Additional data are required to verify the results obtained.

Conclusion

In summary, visceral and contact heat stimuli have been shown to be suitable to generate pain in a clinically applicable manner. VPEP and CHEP seem to indicate drug-induced reduction of pain, which makes them attractive for further studies with the ultimate goal of monitoring analgesia during general anesthesia. The results of the current study offer an approach to measure pain directly and objectively and to monitor visceral and somatosensory pain separately. This may ultimately lead to specific diagnosis and improved treatment of intraoperative pain, and a more specific drug application for the different components of general anesthesia.

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