S(+)-Ketamine Attenuates Increase in Electroencephalograph Activity and Amplitude Height of Sensory-Evoked Potentials During Rapid Opioid Detoxification

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Anesthesia-assisted opioid detoxification offers an opportunity for patients who have undergone unsuccessful conventional detoxifications. Little is known of excitatory effects taking place in the central nervous system during this procedure. Because acute withdrawal is accompanied by *N*-methyl-D-aspartic acid (NMDA)-receptor activation we tested whether the administration of the nonspecific *N*-methyl-D-aspartic acid antagonist S(+)-ketamine results in a reduction of hyperactivity in the central nervous system. Thirty-one patients with a long history of opioid abuse were acutely withdrawn with naltrexone during propofol/clonidine anesthesia and mechanical ventilation. Electroencephalogram (EEG) power spectra as well as median nerve-evoked somatosensory potentials (SSEP) were determined at the following times: evening before detoxification (control), steady-state propofol/clonidine-anesthesia, 30 min after naltrexone administration, and 5 min and 60 min after additional S(+)-ketamine (1.5 mg/kg). Compared to steady-state anesthesia, naltrexone induced a decrease by 270% in the low δ (0.5–3 Hz) and an increase by 110% in the fast β (13–30 Hz) domain of the EEG with only minor changes in the θ-(3–7 Hz) and α-(7–13 Hz) band. Simultaneously, mean amplitude of the late N_{100} peak of the SSEP increased from 3.3 μV to 10.5 μV. The changes could be attenuated by the additional administration of S(+)-ketamine, 5 min and 60 min after injection. Cardiovascular changes were not a reliable index for monitoring acute withdrawal symptoms and determining termination of rapid opioid detoxification. In this regard, EEG power spectra and SSEP were more consistent and clinically useful variables. S(+)-ketamine is a valuable adjunct in the anesthetic regimen, since it attenuates hyperactivity of the central nervous system during rapid opioid detoxification.

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Because of unpleasant and severe withdrawal symptomatology, a large percentage of opiate-dependant patients relapse and return to opiate intake after conventional opiate detoxification (1) (2). In addition, opiate-dependent subjects who undergo classical detoxification in the psychiatric ward experience withdrawal symptoms, usually lasting from 1 to 3 wk (3). Because a large percentage (30%–90%) of patients resumes an opiate habit, alternative therapeutic interventions are being developed. One of these alternatives is rapid opiate detoxification (ROD), a technique in which the patient is anesthetized and the opiate abruptly displaced from the receptor site using an opiate receptor antagonist. For opiate displacement, one of the specific opiate antagonists, such as naloxone (4,5), nalmefene (6), or naltrexone (7), is used. Also, anesthesia is indispensable for the patient to tolerate acute withdrawal symptoms. Sympathetic hyperactivity, with an increase in catecholamines and increase in arterial blood pressure and heart rate (8,9), is managed by the α_2-agonist clonidine (10–12).

Little, however, is known of the changes taking place in the central nervous system (CNS) circuitry during acute withdrawal. Acute detoxification during ROD is characterized by an increase in desynchronization of electroencephalogram (EEG) waves (9,13,14). However, it is not known how to counteract these central excitatory effects.

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Table 1. Daily Dosage and Duration of Drugs Being Abused and Comorbidity of Patients Participating in Rapid Opioid Detoxification

Drugs, comorbidity	Number of patients	Dose (mg/day)	Duration (yr)
Methadone	12	7.8 (2.0–30.0)	3.5 (1–10)
Heroin	19	2.5 (0.5–10.0)	9.7 (5–23)
Marijuana (Δ9-THC)	31	Variable with stop in between	5.5 (10–15)
Nicotine	13	25.8 (20–40)	19 (15–23)
Alcohol	Ø	Ø	Ø
Hepatitis C	17		
Human immunodeficiency virus	7		

Values are mean (range).

We therefore sought to quantify these centrally mediated excitatory effects during ROD, using the EEG and the somatosensory-evoked potential (SSEP). In addition, the potential advantage of the nonspecific *N*-methyl-D-aspartic acid (NMDA)-antagonist S(+)-ketamine to counteract such hyperactivity during ROD was evaluated. The rationale for use of S(+)-ketamine was the known fact of an upregulation in NMDA-receptor activity after long-term use of opiates (15).

Methods

After receiving informed written patient consent and approval by the University Ethical committee, 31 patients were enrolled in the anesthesia-based ROD program (mean ± SD age, 31.7 ± 7.3; male/female = 23/8). Patients had undergone 5 to 10 previous conventional, but unsuccessful, detoxifications. Although 12 patients were participants in an official methadone maintenance program, 19 patients were regular heroin users. Before ROD a detailed clinical history, physical examination, electrocardiogram, and echocardiography were performed. Chest radiography, complete blood chemistry, and urine drug screening were also performed for opiates, cocaine, amphetamine, benzodiazepines, barbiturates, and tricyclic antidepressants.

Because of possible multiple drug interactions (16) patients were only premedicated with oral clonidine 300 μg/70 kg. Anesthesia was induced with midazolam (0.5 mg/kg), shortly followed by propofol (2 mg/kg) and the muscle relaxant atracurium (0.5 mg/kg). After laryngoscopy and tracheal intubation, patients received mechanical ventilation (Evita 4®; Dräger, Lübeck Germany) and their lungs were ventilated with oxygen in air (F_{IO_2} 0.3) to an end-expiratory CO_2 concentration of 38 torr. Anesthesia was maintained with propofol using a drug concentration target controlled infusion system with a target plasma concentration set between 2.4–4.0 μg/mL. Patients also received a continuous infusion of clonidine, which was titrated to maintain heart rate between 50 and 70 bpm and arterial blood pressure between 100 and 120 mm Hg. Cardiovascular variables were monitored continuously via an indwelling radial artery catheter. Central venous pressure was determined via a venous line in the jugular vein, and urine production was measured via a urinary catheter. A continuous infusion of somatostatin (3 mg/24 h) was given to block abstinence-related gastrointestinal hypermotility and hypersecretion (17,18).

For measurement of activity of the CNS, EEG power spectra (μV^2) in the δ- (0.5–3 Hz), the θ- (3–8 Hz), the α- (8–13 H7) and the β-band (13–30 Hz) were derived from position FpZ-C3′ or FpZ-C4′, using platinum stick-on electrodes over a period of 60 s. SSEPs were obtained from the median nerve with the same electrode setting, and a rectangular stimulus (Digi Stim®II, Houston, TX), at an intensity of 1 mA above motor threshold, with a duration of 0.3 ms, and a frequency of 5 Hz. Several hundred sweeps of impulses were averaged over a time period of 150 ms and the peak and the valley values after 50 ms poststimulus were identified by cursor positioning, with automatic computing of amplitude height (μV) and latency (ms).

After steady-state anesthesia, naltrexone was given twice at a dose of 50 mg via a nasogastral tube for opiate reversal at an interval of 1 h. Whenever desynchronization (β-activation) appeared in the EEG, S(+)-ketamine was administered in a dose of 1.5 mg/kg IV.

Arterial blood pressure, heart rate, and EEG power spectra as well as SSEP readings were derived at the following end-points: the evening before detoxification (CONT), at steady-state anesthesia with propofol, 20 min after the second dose of naltrexone, as well as 10 min and 60 min after S(+)-ketamine administration.

After anesthesia, patients were kept in an intensive care unit. There, invasive arterial blood pressure measurement, heart rate and urine production were monitored for 24 h. Also, blood gas analyses were taken repetitively for the detection of any possible hyperventilation, whereas blood samples were analyzed for

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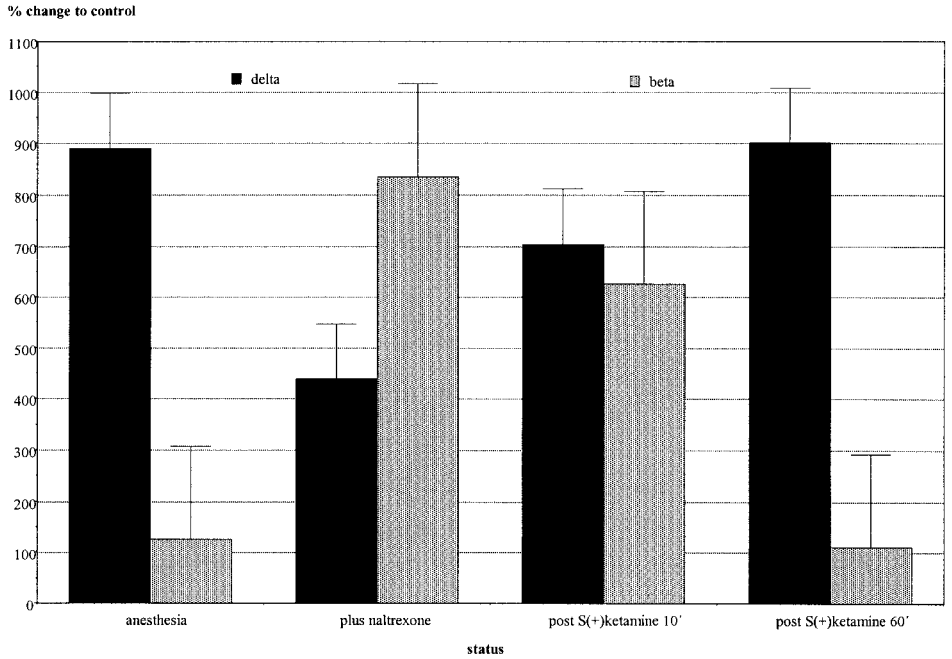

Figure 1. Relative changes of electroencephalographic power (mean ± SD) in the δ- (05–3 Hz) and β- (13–30 Hz) band compared with control in patients undergoing opiate detoxification during anesthesia.

Table 2. Absolute Values in Systolic and Diastolic Blood Pressure (BP) and Heart Rate in Patients Undergoing Rapid Opiate Detoxification (ROD) During Anesthesia (n = 31)

	Control period	Steady-state anesthesia	Plus naltrexone	Plus S(+)-ketamine
Heart rate (bpm)	82 ± 11	58 ± 8†	57 ± 8†	61 ± 8†
Systolic blood pressure (torr)	129 ± 15	122 ± 16	133 ± 13	131 ± 13
Diastolic blood pressure (torr)	76 ± 9	68 ± 10*	74 ± 9	72 ± 8

Values are mean ± SD. * $P < 0.05$; † $P < 0.01$ compared with control.

serum electrolytes to detect magnesium and/or potassium loss, which were corrected by electrolyte replacement as needed. If withdrawal signs became intense and patients complained of pain and/or restless leg syndrome, they were treated with gabapentin in fractional dosages (400-400-400 mg).

Using EEG data and standard deviations from a previous study (19), power analysis yielded a number of at least 30 patients necessary to detect a power change of 50% within the EEG variables, an effect level of 1.0, using an α-error of 5%.

For computation of relative power changes in the various EEG power spectra, the control period was set at 100 and the relative changes at the given end-points were compared with control. In addition to EEG data, absolute values in latency (ms) and amplitude height (μV) of the late N_{100}-peak of the SSEP were determined at the same period as the EEG.

In addition to measurement of variables of CNS activity, absolute values of cardiovascular changes (systolic and diastolic arterial blood pressures and heart rate) were compared with control. Values at different stages during ROD were compared with the control period using analysis of variance for multiple comparisons. A value of $P < 0.05$ was considered statistically significant.

Results

All 31 patients with an ASA status I–II underwent ROD. The mean age was 31.7 yr (range, 21–50 yr), mean weight was 68.7 kg (range, 48–93 kg), and mean height was 174.8 cm (range, 163–186 cm). Duration and dosage of daily opiate abuse in patients were extremely variable (Table 1). Because of their opiate abuse, most patients had undergone several previous unsuccessful detoxifications (range, 5–10). Comorbidity included hepatitis C in 17 patients and acquired immune deficiency syndrome in 7 patients. Although 8 patients reported a previous experience with other illicit drugs such as cocaine and benzodiazepines, they were free from any additional drug intake at the time of admission as determined by urine screening (Table 1).

During the awake control period, the EEG was characterized by a dominance in the α range comprising

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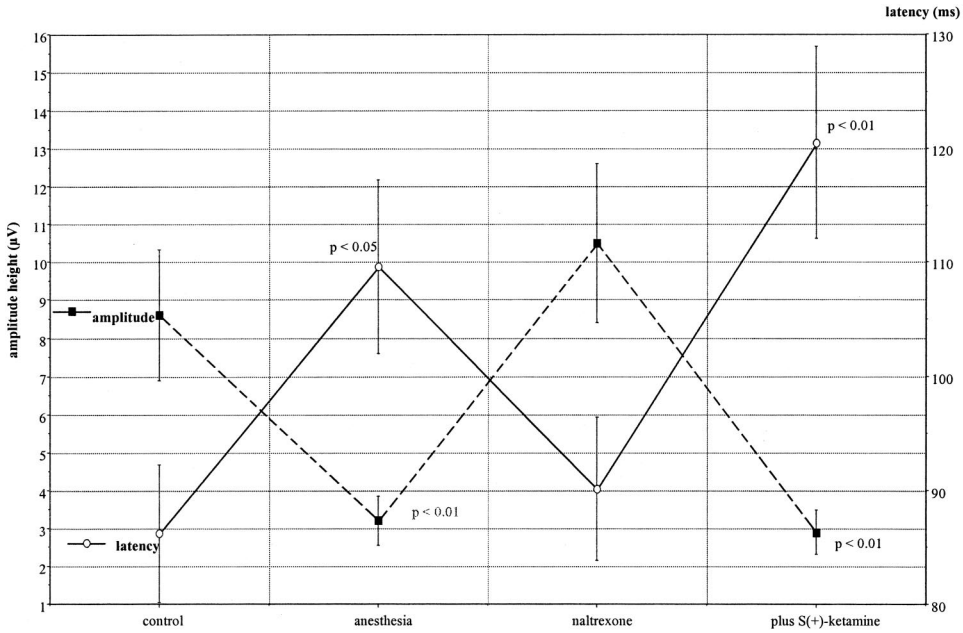

Figure 2. Amplitude height (μV; peak-to-peak) and latency (ms) of the late N_{100}-peak at control and at different stages during rapid opioid detoxification (mean ± SD, n = 31). Significance values are shown compared with control.

50% of the total power, with 17% in the δ- and of 20% in the β- and 13% in the θ-domain. With the induction of anesthesia marked changes in EEG activity were induced. When compared with control there was an increase by 889% in the δ-domain and by 625% in the β-domain (Fig. 1), whereas θ- and the α-band showed reductions of 4% and 44%, respectively. After the administration of naltrexone, relative power in the slow δ-(0.5–3 Hz) band was characterized by an increase of 638% and by 834% in the fast β-(13–30 Hz) domain (Fig. 1). Such changes are highly significant within both power bands ($P <$ 0.001) when compared with control. Power changes in the θ- and α-bands showed decreases of 81% and 31%, respectively, which were not significant when compared with control. The administration of S(+)-ketamine was able to reverse changes in the fast β-domain, resulting in mean relative power of 111% at 60 min after injection (Fig. 1), whereas power in the θ-domain increased to a mean of 115%. When compared with naltrexone, S(+)-ketamine-induced changes of power in the EEG were only significant ($P < 0.05$) in the slow θ- and the fast β-domains ($P < 0.01$; Fig. 1). Increase of power in the slow δ-(+65%) and the α-band (+1%) were not significant when compared with the period after naltrexone administration.

Contrary with EEG changes, naltrexone induced no significant increase in the cardiovascular system (Table 2).

In addition to the EEG, naltrexone induced a significant ($P < 0.01$) increase in amplitude height of the late N_{100}-peak of the SSEP. Compared with steady-state anesthesia with a mean of 3.3 μV, amplitude height increased to a mean 10.5 μV after administration of naltrexone. This increase in amplitude height was reduced by S(+)-ketamine to a mean of 2.9 μV, not significantly different when compared with control (Fig. 2). Also, ROD-induced changes were reflected in the latency of the late N_{100}-peak. Compared with control, anesthesia induced a significant increase ($P <$ 0.05; Fig. 2). After administration of naltrexone, latency values were not significantly reduced compared with steady-state anesthesia (Fig. 2). At 60 min after receiving S(+)-ketamine, latency had increased, with values significantly ($P < 0.05$) different when compared with steady-state anesthesia and highly significant ($P < 0.01$) when compared with control (Fig. 2).

After administration of S(+)-ketamine and once EEG power spectra remained constant for 1 h, anesthesia was terminated. Mean anesthesia time for ROD was 6 h, after which patients were brought to the intensive care unit, where, 2 h later, patients were able to respond to simple questions regarding withdrawal. Symptoms such as gross movements with or without thrashing, as well as muscle and (especially) back pain were reported as intense and treated with incremental dosages of gabapentin. Approximately half of all patients reported intense dreaming with hallucinations, which was experienced as unpleasant only by one third of them.

Discussion

Contrary to McDonald et al. (9), who could not detect any changes in the EEG bispectral index during ROD,

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our data demonstrate a highly significant desynchronization pattern within cortical structures. As suggested by others, the bispectral index is not sensitive enough to detect centrally mediated changes in patients in whom opiates and/or clonidine are present.[1,2] A more detailed analysis within the different power spectra of the EEG seems a prerequisite to detect the sequelae of acute withdrawal.

Also, in contrast to the study of McDonald et al. (9), we observed no increase in arterial blood pressure and/or irregularity in heart rate. From these data it can be concluded that increase in sympathetic tone was successfully eliminated by the use of the α_2-agonist given throughout the entire detoxification procedure. Clonidine therefore seems a mandatory requirement to sufficiently block sympathetically mediated activity within the cardiovascular system in patients undergoing ROD (10,11).

Although attenuating the effects of an increased sympathetic discharge on the cardiovascular system, clonidine was not able to reduce desynchronization with β-activation within the EEG during ROD. In this regard the present data emphasize the favorable use of the unspecific NMDA-antagonist S(+)-ketamine in reversing CNS hyperactivity in an opiate-dependent patient undergoing detoxification. Although ketamine has been demonstrated to reduce morphine tolerance (20), its CNS effects are characterized by a marked acceleration of power within the θ-band when given to volunteers (21) and patients (22,23). Activation of power within the θ-band of the EEG also was seen in the present patient population. But more importantly, application of the NMDA-antagonist resulted in an increase of power in the δ-band and a reduction in augmented power in the β-band. Although β-activation during anesthesia usually denotes an increase in vigilance with memory and awareness (24,25), in the present context, augmentation of β-activity in the EEG suggests increase of activity within the sensory system. Such an increase may stem from demarcation of NMDA-receptor activation (26), an excitatory system that is activated during long-term use of opiates (27). This hypothesis is supported by our data, in which additional administration of S(+)-ketamine, with blockade of NMDA-receptors, induced an attenuation in sensory input, as documented by a reduction of the previously increased amplitude height of the SSEP.

Because SSEP can be used to demonstrate an increase in sensory afferent volleys to pain modulating centers in the CNS (28,29), the increase in amplitude height of the SSEP reflects an increase in sensory activity after the administration of naltrexone (30). Compared with steady-state anesthesia, amplitude height nearly tripled suggesting that such increase in amplitude height may be attributable to an increase in pain transmission (31,32) or even reflect prodromal signs of epileptic seizures (33). In any instance S(+)-ketamine administration was of benefit because it could reverse such neuronal hyperactivity not only in the EEG but also in the SSEP.

Patients who had been given racemic ketamine for anesthesia without a benzodiazepine regularly reported nightmares (34). In the present context, it was interesting to note that among those patients who had experienced vivid dreaming, half of them reported that the dreams were not frightful, but pleasant. This incidence in dysphoria likely was attributable to the lesser simultaneous administration of midazolam, a benzodiazepine, which had been administered during induction of anesthesia. Also, using the active S(+)-isomer of ketamine, a lesser incidence of dysphoric effects could be anticipated (35).

In summary, the present study demonstrates that ROD during general anesthesia induces a hyperexcitatory state of sensory afferents (increase of amplitude height of the SSEP) and a withdrawal-evoked desynchronization of cortical neurons with increase of fast power spectra in the EEG. The addition of S(+)-ketamine to anesthesia-assisted ROD is able to counteract such excitatory effects.

Although a recent article (36) cautioned against the use of general anesthesia for heroin detoxification because of the increased side effects when compared with buprenorphine- or clonidine-assisted detoxification, there are patients who, because of the physical discomfort of withdrawal, are candidates for an anesthesia-assisted ROD procedure. Monitoring of CNS function in addition to use of an NMDA-antagonist may increase the safety of this technique.

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