Concurrent increases in brain electrical activity and intracranial blood flow velocity during low-dose ketamine anaesthesia

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The purpose of the present study was to assess the effects of low-dose ketamine on spontaneous brain electrical activity (EEG) and intracranial blood flow velocity. Twenty healthy volunteers were divided into two groups: Group I (n = 10) received 0.25 mg · kg^{-1} ketamine iv; Group II (n = 10) received 0.5 mg · kg^{-1} ketamine iv. Mean arterial blood pressure (MAP), heart rate (HR), end–tidal PCO_2 ($PETCO_2$), and arterial oxygen saturation (SaO_2) were measured. The EEG was recorded from temporo-occipital recording sites over both hemispheres. Blood flow velocity in the middle cerebral artery was measured using a transcranial Doppler ultrasound system. All variables were evaluated at baseline and for 60 min following ketamine. Administration of ketamine resulted in increases of MAP and HR in both groups to a similar degree. The $PETCO_2$ and SaO_2 did not change in either group over time. Ketamine caused a dose-dependent, transient shift in the EEG to synchronous high-voltage slow waves with an increase in total power (Group I: 301 ±38%; Group II: 104 ± 28%). These changes were associated with dose-dependent increases in mean blood flow velocity (Group I: 35 ± 7%; Group II: 68 ± 10%). Our data suggest that increases in intracranial blood flow velocity are closely correlated to increases in neuronal activity and are not secondary to changes in systemic haemodynamic variables.

Key words
ANAESTHETICS, INTRAVENOUS: ketamine;
BRAIN: blood flow velocity, elctroencephalography;
MEASUREMENT TECHNIQUES: Doppler ultrasound, transcranial.

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Accepted for publication 17th May, 1991.

Le but de cette étude était d'évaluer les effets de petites doses de kétamine sur l'activité electrique spontanée du cerveau (EEG) en corrélation avec le changement de la vélocité du débit sanguin cérébral. Vingt volontaires sains étaient divisés en deux groupes d'une façon randomisée. Le groupe I (n = 10) a recu une dose de 0,25 mg · kg^{-1} de ketamine ; le groupe II (n = 10) a reçu 0,5 mg · kg^{-1} de ketamine par voie intraveineuse. Les paramètres suivants étaient mésurés : la pression arterielle moyenne (MAP), la fréquence cardiaque (HR), la PCO_2 en fin d'expiration ($PETCO_2$) et la saturation artérielle en oxygène (SaO_2). L'EEG était enregistré à l'aide d'électrodes adhésives placées sur la région temporo-occipitale des deux hémisphères. La vélocité du débit sanguin dans l'artère cérébrale moyenne (MCA) était mesurée par un doppler trans-crânien (TCD). Tous les paramètres étaient évalués au début et jusqu'aux 60 minutes après l'application de kétamine. Dans les deux groupes, l'administration de kétamine évoquait une augmentation de la pression artérielle moyenne et de la fréquence cardiaque au même niveau ; la $PETCO_2$ et la SaO_2 n'ont subi aucune modification pendant toute la durée du protocole. Dépendant de la dose appliquée la kétamine a évoqué une modification passagère du tracé EEG vers des ondes synchrones de basse fréquence et un voltage de grande amplitude ainsi qu'une augmentation du spectre de puissance (groupe I : 301 ± 38%; group II : 104 ± 28%). Ces changements étaient associés à l'augmentation de la vélocité du flot sanguin cérébral. Nous concluons que les altérations des paramètres hémodynamiques cérébrales ont une meilleure corrélation avec l'activité neuronale du cerveau et ne sont pas secondaire au changement des paramètres cardiovasculaires.

There is some controversy about the effects of ketamine on brain electrical activity (EEG) and intracranial haemodynamic variables. Ketamine has been reported to depress the thalamic-median nucleus selectively.[1,2] In contrast, Kayama and Iwama[3] found that the administration of ketamine resulted in functional stimulation of both neo-

cortical and hippocampal areas. The effects of ketamine on cerebral blood flow (CBF) and cerebral oxygen consumption ($CMRO_2$) are also controversial.[4–8] Noninvasive transcranial Doppler sonography (TCD) measures blood flow velocity in human basal cerebral arteries continuously.[9,10] Since TCD does not interfere with neurophysiological recordings it may be used to correlate changes in cerebral blood flow velocity with changes in brain electrical activity. The purpose of this study was to evaluate simultaneously the effects of ketamine on EEG and intracranial blood flow velocity.

Methods

Twenty healthy volunteers (ASA physical status I; age: 27 ± 5 yr; female: 12; male: 8) were included in the study. This study was approved by the Institutional Ethics Committee and written informed consent was obtained. The unpremedicated subjects were randomly assigned to one of two groups. Subjects of Group I ($n = 10$) received 0.25 $mg \cdot kg^{-1}$ ketamine *iv* and subjects of Group II($n = 10$) 0.5 $mg \cdot kg^{-1}$ ketamine *iv*. The following variables were recorded at baseline and for 60 min following ketamine administration: EEG, TCD, heart rate (HR, beats/min, RM300™ Honeywell), mean arterial blood, pressure (MAP, mmHg; Dinamap™, Critikon), end–tidal PCO_2 ($PETCO_2$, mmHg; Datex™ Hoyer) and arterial oxygen saturation (SaO_2, %; Nellcor™ Draeger).

EEG

Platinum needle electrodes (13L70, Dantec, Denmark) for EEG recordings were placed in the scalp at C3P3 and C4P4 according to the International 10-20 system. For artifact control, the electro-oculogram (EOG) was recorded from supra- vs infraorbital leads with the bandpass for all recordings set at 0.5–45 Hz. The inter-electrode impedances were kept below 5 kOhm (at 12 Hz). After amplification (BIO-V6™, nbn-electronics, Germany) the EEG and EOG signals were stored on magnetic tape (Store 7-DS™, Racal, Great Britain). Following A/D conversion (ced 1401™ Cambridge Electronics, Great Britain) and digitization (200 Hz sampling rate) EEG segments of 5.2 sec duration were processed by Fast Fourier Transformation (FFT, Kaiser window, -40 dB sidelobe suppression). Spectral power densities for selected frequency bands (delta: 0.5–3.9 Hz, theta: 4.0–7.9 Hz, alpha: 8.0–12.9 Hz, beta: 13.0–45.0 Hz) were calculated from the amplitude spectra.

TCD

Blood flow velocity in the middle cerebral artery (MCA) was measured as reported previously[9,10] using a pulsed transcranial Doppler ultrasound system (TC2-64B™, EME, Germany). The TCD device operates at 2 MHz emitting frequency (pulse repetition: 5–10 Hz, burst width: 13 μsec). The MCA was identified by a transtemporal approach using flow direction discrimination (flow towards the probe), depth control and audio analysis. Following FFT of the Doppler frequency shift, systolic and mean flow velocity (Vsyst, Vmean; $cm \cdot sec^{-1}$) were recorded.

Statistical analysis

All results are expressed as mean ± SEM. Comparisons were made by analysis of variance (ANOVA) for repeated measurements, followed by t tests with Bonferroni corrections. Pearsons's correlation coefficients were calculated between EEG power spectra and TCD data. Statistical significance was assumed at a $P \leq 0.05$.

Results

All subjects became unconscious within 73 ± 15 sec after ketamine administration. Onset of unconsciousness was not different between groups. Data for HR, MAP, SaO_2 and $PETCO_2$ are shown in the Table. In both groups HR and MAP increased within two minutes following ketamine without intergroup differences. Haemodynamic baseline values were regained after 7 ± 1 min (Group I) and 13 ± 3 min (Group II), respectively. The SaO_2 did not change over time and $PETCO_2$ remained constant within each group.

EEG

In seven subjects of Group I and eight of Group II dominant alpha-activity was present during baseline recordings. In all other subjects dominant frequency extended from fast theta to alpha frequency (6–12 Hz). Following ketamine administration, alpha-activity was decreased by 79 ± 8% in both groups. At the same time synchronous high-voltage theta-activity was recorded in both groups. Theta power increased by 89 ± 11% in Group I and by 229 ± 29% in Group II. This was associated with dose-dependent increases in delta- (Group I: 34 ± 6%; Group II: 154 ± 13%) and beta-activity (Group I: 25 ± 4%; Group II: 54 ± 6%). As a result, total EEG-power was increased in both groups (Figure 1). In Group I this increase in total power faded within 6 ± 2 min and in Group II within 14 ± 4 min.

TCD

Following ketamine administration Vmean increased by 35 ± 7% in Group I and by 68 ± 10% in Group II ($P < 0.05$) (Figure 2). The Vmean was different between the groups at 2 to 12 min following ketamine administration ($P < 0.05$). In Group I Vsyst did not change over time. In Group II Vsyst increased by 45 ± 9% within two to five min following ketamine ($P < 0.05$). In group I baseline

TABLE

	HR ($b \cdot min^{-1}$)		*MAP* (*mmHg*)		SaO_2 (%)		$PETCO_2$ (*mmHg*)	
Group	*I*	*II*	*I*	*II*	*I*	*II*	*I*	*II*
t(min)								
0	70 ± 4	68 ± 5	87 ± 4	88 ± 4	99 ± 1	98 ± 1	41 ± 1	44 ± 2†
2	90 ± 5*	95 ± 6*	104 ± 5*	107 ± 5*	99 ± 1	98 ± 1	39 ± 1	45 ± 2
4	99 ± 8*	101 ± 9*	106 ± 5*	110 ± 5*	98 ± 1	99 ± 1	38 ± 1	45 ± 2
6	94 ± 8*	105 ± 9*	101 ± 5*	107 ± 5*	99 ± 1	98 ± 1	39 ± 1	46 ± 3
8	89 ± 4*	101 ± 10*	97 ± 4*	104 ± 5*	98 ± 1	99 ± 1	40 ± 2	44 ± 2
10	76 ± 4	94 ± 7*	94 ± 4*	101 ± 5*	98 ± 1	98 ± 1	39 ± 1	43 ± 2
15	73 ± 4	85 ± 6*	90 ± 4	97 ± 5*	99 ± 1	99 ± 1	39 ± 2	44 ± 2
20	75 ± 4	76 ± 5	91 ± 4	96 ± 4*	99 ± 1	99 ± 1	40 ± 1	44 ± 2†
60	69 ± 5	74 ± 4	92 ± 4	90 ± 3	99 ± 1	98 ± 1	41 ± 2	45 ± 2

Heart rate (HR), mean arterial blood pressure (MAP), arterial oxygen saturation (SaO_2) and end-tidal PCO_2 ($PETCO_2$) following low-dose ketamine (mean ± SD). Group I ($n = 10$): ketamine 0.25 $mg \cdot kg^{-1}$; Group II ($n = 10$): 0.50 $mg \cdot kg^{-1}$ ketamine; significance: * vs baseline within group; † vs Group I at each respective time level; $P < 0.05$).

data were reestablished within 9 ± 3 min. Vsyst and Vmean were increased over a period of 15 ± 4 min following ketamine in Group II.

Correlation between EEG and TCD

The correlation of increases in theta-activity and Vmean was r = 0.79 ($P < 0.01$) in Group I and r = 0.86 ($P < 0.01$) in Group II. Correlations between MAP and Vmean were r = 0.41 ($P > 0.05$) in Group I and r = 0.49 ($P > 0.05$) in Group II.

Discussion

In the present study, ketamine produced dose-dependent increases in delta-, theta-, and beta-activity. This was paralleled by dose-dependent increases in MCA blood flow velocity. These changes were not correlated with systemic haemodynamic changes or variations in $PETCO_2$. Our results suggest that ketamine-induced increases in Vmean are produced by neuronal activation.

In contrast to most other anaesthetics, the anaesthetic effects of ketamine are associated with activation of cerebral function resulting in synchronized theta- and desynchronized beta-activity. Kayama and Iwama reported the appearance of synchronous high-voltage slow wave activity following ketamine (2 to 5 $mg \cdot kg^{-1}$) in unrestrained cats.[3] In agreement with previous studies,[11] ketamine decreased alpha-activity and increased theta-activity with smaller increases in delta- and beta-activity. The EEG slow waves following short-lasting desynchronization has been interpreted as a correlate of ketamine-induced seizure activity in subcortical and neocortical areas.[3,12] Even though no spike-and-wave complexes as an indicator for the occurrence of seizure activity or electrical correlates of myocloni were observed, the twitching of face or limb muscles seen in some volunteers may be related to these electrical phenomena.

The effect of ketamine on cerebral metabolism is controversial.[4–8] It has been shown that increases in EEG activity are associated with increases in neuronal metabolism.[13,14] Since cerebral metabolism was not measured in the present study it remains speculative if the appearance of high-voltage hypersynchronuous slow-wave activity are related to ketamine-induced cerebral metabolic stimulation.[4,7]

Ketamine has been found to cause variable CBF changes, from an 80% increase[4] to a 50% decrease.[5,6] Discontinuous CBF measurements may result in decreased sensitivity to transient changes in cerebral haemodynamics. Here, we continuously recorded intracranial blood flow velocity using noninvasive TCD-monitoring.[9,10] The dose-dependent increases in MCA blood flow velocity cannot be explained by changes in HR, MAP. Even though $PETCO_2$ was different between groups it did not change over time in either group. In humans the cerebral vascular response to CO_2 is not altered by ketamine.[15] Our results are thus consistent with the view that ketamine alters cerebral haemodynamics due to its cerebral rather than to its peripheral vascular effects.[10] Even though this response is not strictly linear the present study demonstrates that increases in blood flow velocity are correlated with increases in theta-activity and EEG total power. Together, our data indicate concurrent stimulation of both neuronal activity and cerebrovascular haemodynamics.

The CBF cannot be measured directly using TCD because the diameter of the insonated vessel segment

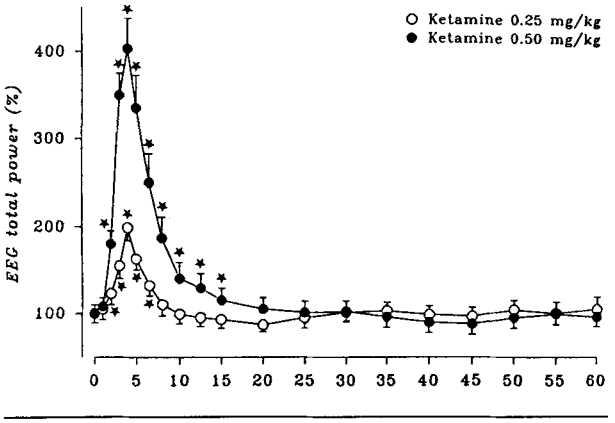

FIGURE 1 Percent changes in EEG total power (upper graph) following low-dose ketamine compared with baseline recordings (100%). Group I: ketamine 0.25 $mg \cdot kg^{-1}$; Group II: ketamine 0.5 $mg \cdot kg^{-1}$ ($*P < 0.05$ compared with baseline).

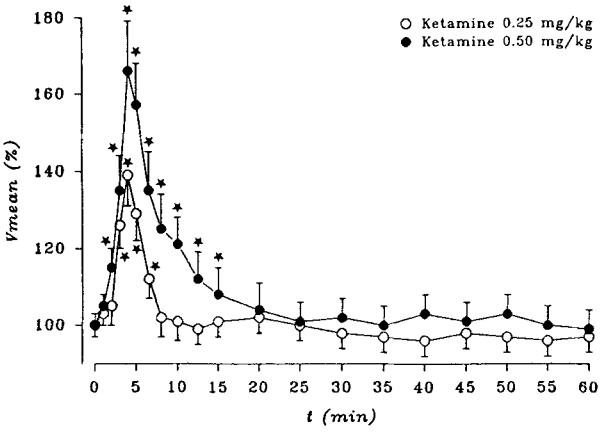

FIGURE 2 Percent changes in MCA blood flow velocity (Vmean) following low-dose ketamine, compared with baseline recordings (100%) Group I: ketamine 0.25 $mg \cdot kg^{-1}$; Group II: ketamine 0.5 $mg \cdot kg^{-1}$ ($*P < 0.05$).

(MCA) is unknown. However, experimental studies using anaesthetics and narcotics have shown that changes in CBF are correlated to changes in Vmean.[16,17] The present experiments indicate only minor changes in the diameter of the proximal MCA under these conditions. Our data suggest that dose-dependent changes in Vmean following ketamine reflect relative CBF changes since the insonation angle and depth of insonantion were maintained constant over time and systemic hemodynamics were not different between groups. It is possible that MCA blood flow velocity changes following ketamine are not related to hemodynamic effects of the drug but to changes in neuronal activity.

Our study demonstrates that 0.25 $mg \cdot kg^{-1}$ and 0.50 $mg \cdot kg^{-1}$ ketamine produces stimulation of brain electrical activity in parallel to dose-dependent increases in intracranial blood flow velocity. The authors conclude that simultaneous recordings of brain electrical activity and cerebral blood flow velocity may be a valuable tool for continuous monitoring of anaesthetic-induced changes of both functional and cerebral haemodynamic variables.

Acknowlegement

The authors would like to thank Dr. Irmgard Blanc for her help in editing the manuscript.

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