Ketamine-induced Electroconvulsive Phenomena in the Human Limbic and Thalamic Regions

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In nine patients with cortical, limbic and thalamic electrode implants, correlating electrical activity and gross behavior were observed following administration of ketamine, 70 per cent N₂O, and thiopental. Ketamine was administered in four dosages: 0.5, 1, 2, and 4 mg/kg. One patient who received 0.5 mg/kg iv manifested depth-electrode seizure activity without loss of consciousness. Two patients, receiving 1 mg/kg iv, developed increased frequency in their depth-electrode EEG’s with transient unconsciousness. All six patients receiving 2 or 4 mg/kg iv developed electrical seizure activity in the limbic and thalamic areas, with uncorrelated behavioral manifestations ranging from apparent “unconsciousness” and immobility to actual tonic and clonic motor activity. The surface EEG did not manifest the intense electrical activity in the limbic region at all times. In contrast, administration of 70 per cent N₂O and 400 mg thiopental did not induce electrical seizure phenomena. It is suggested that ketamine be used cautiously in patients with seizure disorders. (Key words: Ketamine; Hypothalamus; Limbic; Thalamic; Hippocampus; Hippocampal gyrus; Hypersynchrony; Thalamoneocortical; Cataleptic.)

The neuropharmacologic effects of ketamine have been extensively studied in lower animals. Myasaka and Domino demonstrated in cats that ketamine-induced anesthesia was associated with slow-wave activity in the thalamoneocortical area, but with no altered activity in the hypothalamus. They have labeled ketamine a “dissociative anesthetic.” In similar neuropharmacologic studies by Winters et al., the reticular activating system was found to be stimulated by ketamine, an effect unlike that of thiopental and halothane, which depressed synaptic transmission in this area. Hypersynchronous wave patterns similar to that induced by hallucinogens and CNS stimulants occurred after ketamine. In higher doses, limbic and hypothalamic seizures were demonstrated while the animal appeared immobile and analgesic (cataleptic stage). Because of the cataleptic behavior at a time certain areas of the central nervous system are stimulated, Mori has suggested the use of the term “cataleptic anesthesia” in place of “dissociative anesthesia.”

Neuroelectric studies in man employing surface-electrode electroencephalography demonstrated hypersynchronous wave patterns during the analgesic stage of ketamine similar to the hypersynchronous waves seen in animals. Clinically, there have been reports of hyperactive reflexes, inappropriate movements, active laryngeal-pharyngeal reflexes, and the occurrence of emergent psychic effects. These findings are more reminiscent of the action of excitatory agents such as phencyclidine, mescaline, and LSD than of a depressant drug such as thiopental.

The purpose of this study was to clarify further the neuromechanism of ketamine in man. We wished first to see whether the “dissociation” seen in cats does occur in man; second, whether surface encephalography reflects the changes seen in the limbic and thalamic areas; third, to compare the effect of ketamine with those of a known CNS depressant (thiopental) and a weak analgesic (N₂O).
Method

At the University of California Brain Research Institute, patients with seizure disorders are studied by depth-electrode encephalography. By stereotaxic technique, electrodes are implanted bilaterally and symmetrically in the limbic region (amygdala), hippocampus (anterior, middle and posterior pes) and hippocampal gyrus (anterior, middle and posterior gyrus). The radiologic appearance of the depth electrodes is shown in figure 1. Electroencephalographic activity from the cortex is monitored by electrodes implanted in the skull in the international 10–20 EEG distribution.7

The electrodes are placed in the brain for four to six weeks for localization of seizure foci. During this time the patient remains hospitalized. Control EEG’s with the patient awake and during sleep and spontaneous seizure activity are recorded by use of radiotelemetry.8 When the epileptic focus is localized, the patient is scheduled for operative ablation of the area.

During the two to four weeks that the electrodes were implanted in such patients, we investigated the EEG effects of ketamine, thiopental, and N2O. All patients were fully informed concerning the procedures and consented to the study. The investigation was approved by the Clinical Neurophysiology Program Advisory Committee of the Brain Research Institute.

Nine epileptic patients, ages 17 to 37 years, were used as subjects. Two weeks after implantation of electrodes, electroencephalograms were obtained during the awake–interictal state, as well as during spontaneous seizure activity. The patients were then exposed to the effects of nitrous oxide and thiopental to serve as a basis for comparison with ketamine. Nitrous oxide, 70 per cent, was administered by mask until electroencephalographic alterations occurred or until behavioral changes necessitated termination of administration. Oxygen, 100 per cent, was then administered, and the patient was allowed to recover spontaneously. Twenty minutes after recovery from nitrous oxide, thiopental, 400 mg, was given intravenously. Oxygen and intermittent positive-pressure ventilation were begun if the patient became apneic. Depth and surface electroencephalograms were observed continuously during administration of any agent.

Approximately one to two weeks after exposure to nitrous oxide and thiopental, the patient received ketamine anesthesia for surgical removal of the electrodes.

All patients received 10 mg morphine SO4 and 0.4 mg scopolamine as preoperative medication. The radial artery and internal jugular veins were catheterized to obtain samples for ketamine plasma levels. The EEG was monitored by radiotelemetry. After control EEG and blood samples were obtained, ketamine was administered in single doses intravenously in one of the four dosage schedules (0.5, 1, 2, and 4 mg/kg). Blood samples from four subjects were successfully obtained simultaneously from the internal jugular vein and the radial artery at 1, 2, 3, 4, 5, 10, 15, and 30 minutes for determination of plasma ketamine level by the gas–liquid chromatographic technique of Hodson et al.9 Oxygen and positive-pressure ventilation were administered if the patient became apneic or if seizure activity occurred.

Results

Changes with 70 Per Cent Nitrous Oxide

Inhalation of 70 per cent N2O produced a variety of behavioral responses, varying from mild restlessness to frank hallucinations. None of the patients had total loss of consciousness. An increase in the frequency of electrical activity (15–20 Hz) recorded from the depth electrodes was the only EEG change noted. An example of depth-electrode EEG changes during nitrous oxide administration is shown in figure 2. These changes have also been observed in a similar study in cats by Winters.10

Changes with 400 mg Thiopental IV

Immediately after thiopental, 400 mg iv, every patient had complete loss of consciousness as expected and a coincident occurrence of irregular high-amplitude (200–400 μV), slow (3–4 Hz) waves in both cortical and depth electrodes. An example is shown in figure 3.
ADMINISTRATION OF KETAMINE

Table 1 summarizes the effects of ketamine.

Changes after 0.5 mg/kg iv: The only patient who received this dose had transient loss of consciousness, increased muscle tone, and no analgesia to pin prick. Even with such a small dose, there were marked electrical changes in the limbic and thalamic regions, as shown in figure 4. However, this patient was having frequent spontaneous electrical seizures. It is possible that these seizures following ketamine were coincidental spontaneous seizures.

Changes after 1 mg/kg: 1 mg/kg iv produced transient loss of consciousness in one patient. The other patient remained awake and did not have analgesia. In both patients there were increases in the frequencies of EEG waves to 30-50 Hz, but no seizure activity was evident (fig. 5).

Changes after 2 and 4 mg/kg: The six patients who received these doses showed a variety of behavioral manifestations such as apparent immobility and “loss of consciousness,” hyperextension of the body, increased muscular tone, and jerking tonic-clonic muscular movements, as shown in table 1. All six patients had electrical seizure activity like that exemplified by figure 6, which shows seizure activity occurring 90 seconds after ketamine. This appeared first in the left midgyrus and finally spread to almost all areas except the cortex. Figure 7 typifies the postictal depression that followed these electrical seizure bursts.

The levels of ketamine in arterial and internal jugular venous blood after 2 mg/kg iv are shown in figure 8, and after 4 mg/kg iv, in figure 9. The electroconvulsive phenomena coincided with peak concentrations in arterial and internal jugular venous blood.
Fig. 2. EEG changes in the limbic and thalamic regions following 70 per cent N₂O. The only change in both depth and cortical EEG's is a slight increase in frequency in the right mid pes accompanied by behavioral manifestations of the effect of N₂O. (Patient 4.)
B.M. 24 yrs old 9 8-4-71

L. ANT GYRUS
L. MID GYRUS
RT. AMYG
RT. ANT PES
RT. MID PES
RT. ANT GYRUS
RT. MID GYRUS
C3-P3

CONTROL, AWAKE AND ORIENTED

100 µV
1/sec

14 sec AFTER PENTOTHAL, UNCONSCIOUS, APNEIC

4 min AFTER PENTOTHAL, UNCONSCIOUS, APNEIC, VENTILATED WITH 100% O2

8 min AFTER PENTOTHAL, AWAKE AND ORIENTED, BUT HAS SLURRED SPEECH

Fig. 3. Changes induced by thiopental, 400 mg iv. There is rapid induction of high-amplitude (200–400 µv) slow waves (3–4 Hz) in all leads, coinciding with loss of consciousness and respiratory depression. Eight minutes later, a residual effect is still evident in both the EEG and behavior. No patient had isolated bursts of seizure activity. Left central parietal region, C3-P3. (Patient 4.)
Fig. 4. Seven minutes after ketamine, 0.5 mg/kg iv, seizure activity similar to a spontaneous seizure pattern is evident in the right anterior gyrus. Note that the cortical leads (F7-T3, F8-T6, C4-P4) do not manifest the marked changes in the depth electrodes. Left frontotemporal, F7-T3, right frontotemporal, F8-T6, right central parietal, C4-P4. (Patient 3.)
Fig. 5. Eighty seconds after ketamine, 1 mg/kg iv, there is increased frequency in right mid pes only. The patient did not lose consciousness, but became restless and confused, necessitating administration of thipental for induction of anesthesia. (Patient 5.)
AUGUST 1971, B.M., 24 YR. OLD Q

LT ANT GYRUS
LT MID GYRUS
RT AMYG
RT ANT PES
RT MID PES
RT ANT GYRUS
RT MID GYRUS

CONTROL INTERICTAL

SPONTANEOUS SEIZURE ACTIVITY, BIZARRE BEHAVIOR

100 µV

1 sec

LT MID PES
LT ANT GYRUS
LT MID GYRUS
RT AMYG
RT ANT PES
RT MID PES
RT ANT GYRUS
RT MID GYRUS

PREMEDICATED. APPEARS CALM ON ARRIVAL AT O.R.

90 sec AFTER KETAMINE APNEIC, CATATONIC

1 sec
KETAMINE-INDUCED ELECTROCONVULSIVE PHENOMENA

MARCH 1971  N.B.  19  YR.  OLD  Q

LT MID PES
LT POST PES
RT AMYG
RT POST PES
RT ANT GYRUS
RT POST GYRUS

CONTROL INTERICTAL

SPONTANEOUS SEIZURE ACTIVITY

100 µV

1 sec

PREMEDICATED, APPEARS CALM ON ARRIVAL AT O.R.

2 min AFTER KETAMINE

APNEIC AND CATATONIC

KETAMINE BLOOD LEVEL 1.22 µg/cc

Fig. 6 (facing page) and Fig. 7. Changes after ketamine, 2-4 mg/kg iv. Figure 6 shows the onset of electrical seizure activity in the left mid gyrus and its spread to other limbic and thalamic areas. The cortical electrodes (C3-P3) do not reflect seizure activity. (Patient 4.)

Figure 7 typifies the postulate depression occurring after induced electrical seizure activity. Again, the cortical leads (T3-P3) do not manifest seizure activity. Left central parietal region, C3-P3; left temporoparietal region, T3-P3. The patient's behavior was characterized by immobility and catatonia without tonic or clonic convulsion during the intense electrical activity. (Patient 1.)
Table 1. Summary of Behavioral and EEG Changes Induced by Ketamine

<table>
<thead>
<tr>
<th>Dose of Ketamine (mg)</th>
<th>Limbic and Thalamic Electrical Activity</th>
<th>Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg/kg Patient 3</td>
<td>Seizure activity</td>
<td>Confused and restless; no loss of consciousness</td>
</tr>
<tr>
<td>1 mg/kg Patient 5</td>
<td>Frequency increased from 30 to 50 Hz</td>
<td>No loss of consciousness</td>
</tr>
<tr>
<td>1 mg/kg Patient 9</td>
<td>Frequency increased from 15 to 30 Hz</td>
<td>Transient loss of consciousness</td>
</tr>
<tr>
<td>2 mg/kg Patient 1</td>
<td>Seizure activity</td>
<td>Tonic–clonic motor activity</td>
</tr>
<tr>
<td>2 mg/kg Patient 2</td>
<td>Seizure activity</td>
<td>Apnea, hyperextension</td>
</tr>
<tr>
<td>2 mg/kg Patient 4</td>
<td>Seizure activity</td>
<td>Increased muscular tone; apnea; difficult to intubate</td>
</tr>
<tr>
<td>2 mg/kg Patient 8</td>
<td>Seizure activity</td>
<td>Jerking motor movements; clonic motor activity</td>
</tr>
<tr>
<td>4 mg/kg Patient 6</td>
<td>Seizure activity</td>
<td>Patient immobile, appears asleep</td>
</tr>
<tr>
<td>4 mg/kg Patient 7</td>
<td>Seizure activity</td>
<td>Tonic–clonic motor activity</td>
</tr>
</tbody>
</table>

Discussion

In this study, ketamine was administered to patients who had depth electrodes implanted in the limbic and temporal regions. Although electrical activity in such areas has been studied in animals, to our knowledge this is the first observation of electrical activity in the limbic system and thalamus during administration of ketamine to man. The results of the animal studies and those of our study of man are quite similar, in that there were pronounced increases in the electrical activity in the limbic area in both. In some patients, especially those who received 2–4 mg/kg iv doses, the activity progressed to electrical seizure phenomena.

Each of our patients had been diagnosed as epileptic. Although their underlying disorder may have influenced the seizure activity following ketamine, the consistent observation of limbic and temporal electrical seizure activity after ketamine strongly suggests that ketamine excites the subcortical areas. In contrast, administration of thiopental produced classic depression, characterized by high-amplitude slow waves without electrical seizures in the limbic and thalamic areas.

For many years, all anesthetics were considered CNS depressants. More advanced neurophysiologic studies of anesthetic effects in animals by several investigators have demonstrated that there is no unified mode of action of general anesthetics. Some drugs considered to be anesthetics, such as gamma-hydroxybutyrate, phencyclidine, trichloroethylene, diethyl ether, and ketamine, induce a continuum of cortical and subcortical EEG changes consistent with CNS stimulation. This was further correlated with stimulation or lack of depression of the reticular formation. Paradoxically, animals became catatonic or appeared immobile during this period. Our present study in man confirmed that this paradoxical condition can occur, in that the patient may appear immobile and “anesthetized” with ketamine while electrical seizure activity is occurring in the limbic and thalamic regions. Unfortunately, the electrical activity in the limbic and thalamic regions is not always reflected in the conventional surface or scalp EEG. Thus, in the large number of patients
Fig. 8. Plasma levels of ketamine as determined by gas chromatography during 30-minute period after administration of 2 mg/kg iv. (Patient S.)

S.N. 33yr ♀
2mg/kg Ketamine
I.V. at time 0

Fig. 9. Plasma levels of ketamine as determined by gas chromatography during 30-minute period after administration of 4 mg/kg iv. (Patient L.)

L. S. 37yr ♂
4mg/kg Ketamine
I.V. at time 0
who ordinarily receive ketamine, monitoring the surface EEG does not help to diagnose the possibility that the patient is having limbic and thalamic seizures. Only when seizure activity reaches the cortex does the surface EEG grossly change, and by this time the patient is usually manifesting convulsive behavior. The abnormal muscle movements frequently seen with ketamine may indicate that limbic and thalamic seizure activity is occurring despite absence of gross surface EEG changes consistent with a seizure.

Previous studies of ketamine indicative of its ability to induce cerebral excitation have shown: 1) its consistent ability to increase both the rate of cerebral O_2 consumption and cerebral blood flow, in contrast to the decrease of both values after thiopental; 2) the high incidence of vivid dreams, hyperexcitability and/or psychomotor activity; 3) the marked increase in CSF pressure.

Because of the results we obtained in this study, we believe that ketamine should be used with caution or not at all for patients who have seizure-related disorders, since its administration may result in aggravation of the already hyperexcitable central nervous system. As cited in an editorial on ketamine by Winters, "If gross seizures do occur during its administration in both epileptic and non-epileptic patients, further administration of ketamine to "deepen" the anesthesia should be avoided, and instead, a known general CNS depressant such as a barbiturate or a limbic depressant such as Diazepam prescribed."

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References


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