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EFFECTS OF KETAMINE ON EEG ACTIVITY IN CATS AND MONKEYS[1]

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Ketamine or dl-2-(o-chlorophenyl)-2-(methylamino)-cyclohexanone hydrochloride is a rapid-acting general anesthetic that is administered intravenously or intramuscularly. Since its introduction in 1968 there has been considerable controversy on the nature of Ketamine anesthesia. Ketamine was defined by Corssen *et al.* (1968) as a dissociative anesthetic because of its differential effect upon neocortical, thalamic and limbic structures. These findings were later challenged by Mori *et al.* (1971) and by Winters *et al.* (1972). They felt that Ketamine was a stimulant anesthetic and that it produced a catatonic state. Recently Bennett *et al.* (1973) and Ferrer-Allado *et al.* (1973) have suggested that Ketamine may precipitate and/or aggravate seizures in epileptic patients. The present study has been carried out in 28 cats and 6 monkeys in an attempt to assess the effect of Ketamine on the cortex of normal and epileptic animals.

METHODS

Cats were anesthetized with ether. Following the surgical procedure for exposure of both hemispheres, ether anesthesia was discontinued and the animals were immobilized with gallamine and artificially ventilated. Wound edges and pressure points were anesthetized with local infiltration of procaine hydrochloride. Additional local anesthesia was given as required to maintain the animals free of pain. If not otherwise specified, Ketamine was given intravenously.

Recordings from the surface of the cerebral cortex were carried out with silver ball electrodes held in an adjustable carrier. The hippocampus was explored stereotaxically with a multicontact depth probe. The position of the probe was later confirmed at autopsy. The reference electrode for monopolar recordings consisted of a small alligator clip clamped to the bone of the frontal sinus. EEG recordings in monkeys were obtained with silver–silver chloride electrodes applied to the scalp with collodion. The electrode impedance was always less than 5 kΩ. The animals were placed in a Foringer monkey chair for the duration of the experiment. The input from the electrodes was led into 8 Grass P511 preamplifiers adjusted to a bandwidth from 0.3 c/sec to 1 kc/sec. The output from the preamplifiers was entered simultaneously into a Tektronic 565 oscilloscope, a Sanborn tape recorder, a Fabritek 1052 averager and an Offner type T electroencephalograph. Write-outs from the averager were made with a Moseley X–Y plotter.

Blood pressure was monitored via a catheter inserted into the femoral artery with a Statham pressure gauge and a DC preamplifier. Epileptic foci were produced by intracortical injection of penicillin. Aqueous solution of potassium penicillin, 400,000 units/ml, mixed with a drop of methylene blue was used. The intracortical injection was carried out with a unimetric microsyringe held in a stereotaxic carrier. With the aid

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of a Zeiss dissecting microscope and micromanipulator the needle was inserted into the cortex 1.0–1.5 mm. 0.010 ml of penicillin were injected to produce a subpial blue halo 1–1.5 mm thick around the needle. Epileptogenic spikes were automatically analyzed via a Mentor spike analyzer. The analyzer is a differential amplitude discriminator with two adjustable threshold levels. The levels form a variable "window" so that only spikes with a peak amplitude falling between the two levels generate an output. Each spike detected by the analyzer provides at 0.5 msec, 1 V output pulse which was fed into an electronic counter and a Fabritek 1052 minicomputer. The latter computed the spikes into frequency histograms. The penicillin spikes were of sufficient amplitude that could easily be differentiated in this fashion from the background activity.

RESULTS

Effects of Ketamine on electrocorticogram

The effect of Ketamine was studied in 18 cats. The changes in the electrocorticogram produced by Ketamine were dose related. Doses of Ketamine below 5 mg/kg induced generalized beta activity of 26–34 c/sec and 70–200 μV in amplitude. This beta rhythm differentiated itself from the beta already present before Ketamine by its higher amplitude and tendency to appear in spindle-like bursts (see Fig. 1). The most dramatic changes, however, occurred at doses of 5 mg or more per kg and consisted of bursts of hypersynchronous beta intermixed with slow wave complexes. These slow wave complexes will be called "Ketamine complexes" (KCs). KCs had two different morphological appearances. Frequently they resembled polyspike-slow

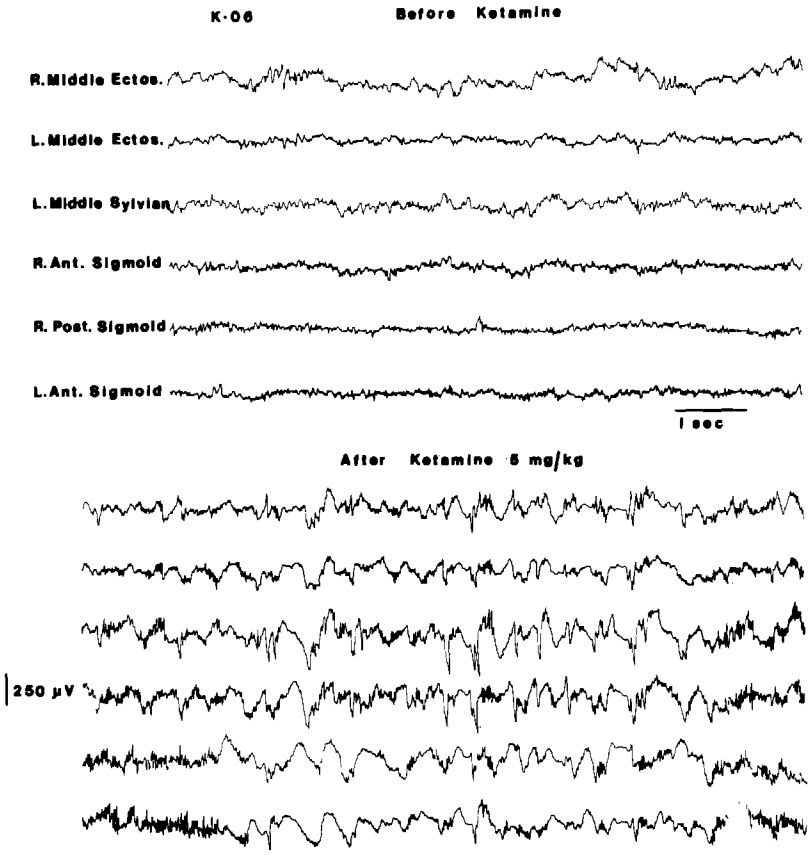

Fig. 1. Effect of Ketamine on the electrocorticogram of cat K-06. The upper half of the figure represents the activity of waking state; the lower half the activity following the administration of Ketamine 5 mg/kg. Unipolar recording reference to the bone of the frontal sinus.

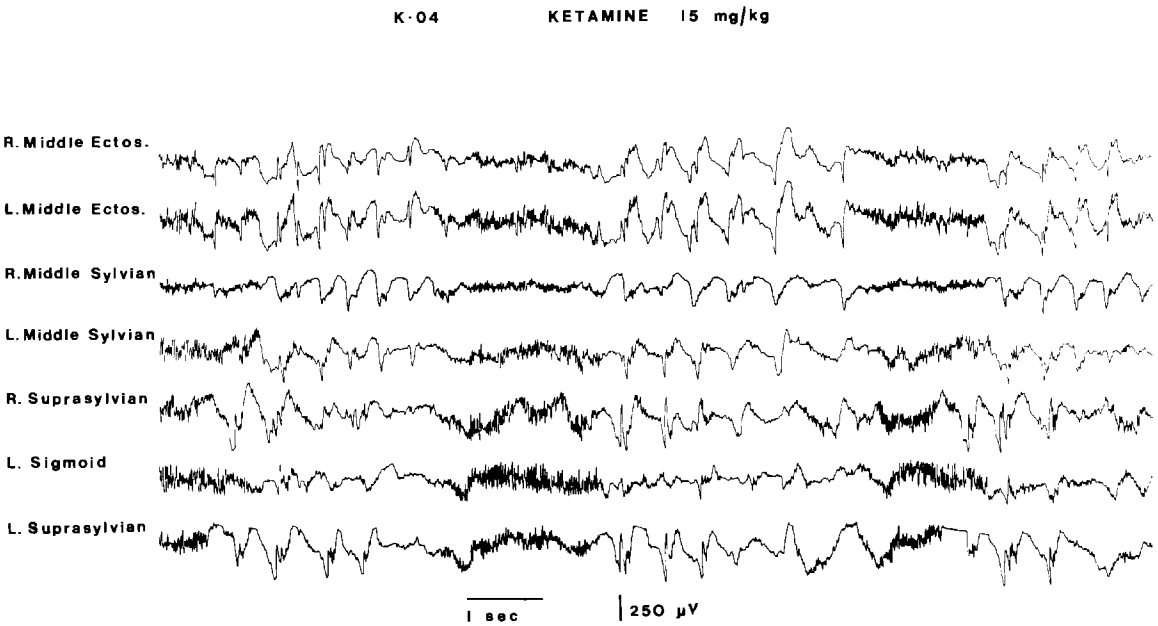

Fig. 2. Electrocorticogram during Ketamine anesthesia. Note the alternating bursts of polyspikes-slow waves and bursts of high voltage synchronous beta. Unipolar recording reference to the bone of the frontal sinus.

wave complexes (Fig. 1 and 2), the slow waves being associated in their rising or descending slopes with spikes and polyspikes. They had an amplitude of 200–500 μV and a frequency of 0.5–2 c/sec and appeared over all cortical regions either slightly asynchronous or as seen in Fig. 2 bilaterally synchronous. In 4 cases, as shown in Fig. 2, Ketamine complexes occurred in bursts alternating with bursts of hypersynchronous beta in a quasi-periodic fashion. The presence of polyspikes and spikes is better shown in Fig. 3 from a photograph of oscilloscopic tracings in 2 cats. In the same figure we see the second type of KCs, that is high voltage beta activity on top of slow waves (see also Fig. 4). Often it was morphologically uncertain to determine if KCs represented a combination of beta–delta waves or true polyspike-slow waves. After doses of 5 mg/kg KCs were seen for 5–30 min. Doses greater than 15 mg/kg produced similar changes with longer durations up to 2–3 h. Gradually KCs became less frequent, then disappeared while the hypersynchronous beta activity became continuous. The above described neocortical patterns were also observed in the hippocampus.

Two recordings were carried out from the scalp of unrestrained cats to correlate behavior with EEG changes. During KCs the cats were unresponsive and in a catatonic state with eyes opened, mildly mydriatic pupils and opisthotonic posture. Occasional licking movements of the tongue were seen. No convulsive movements were noted. When hypersynchronous beta activity was the major feature of the tracings, the cats had their eyes open, nystagmus, continuous licking movements and swinging of the head as in an attempt to move. When they attempted to walk severe ataxia was present.

The effect of Ketamine was also studied in 6 *Macaca rhesus*. In these monkeys Ketamine was given intramuscularly. Low doses (10–15 mg/kg) of Ketamine produced generalized 4–6 c/sec theta and beta activity. Higher doses usually above 20 mg/kg induced the presence of generalized quasi-periodic sharp-slow wave complexes of 0.5–1 c/sec and 100–200 μV in amplitude (see Fig. 5). These complexes are strikingly similar to the complexes seen in subacute sclerosing panencephalitis. No difference could be detected in the "catatonic state" of the monkeys between the period characterized by beta activity and the periods with quasi-periodic complexes.

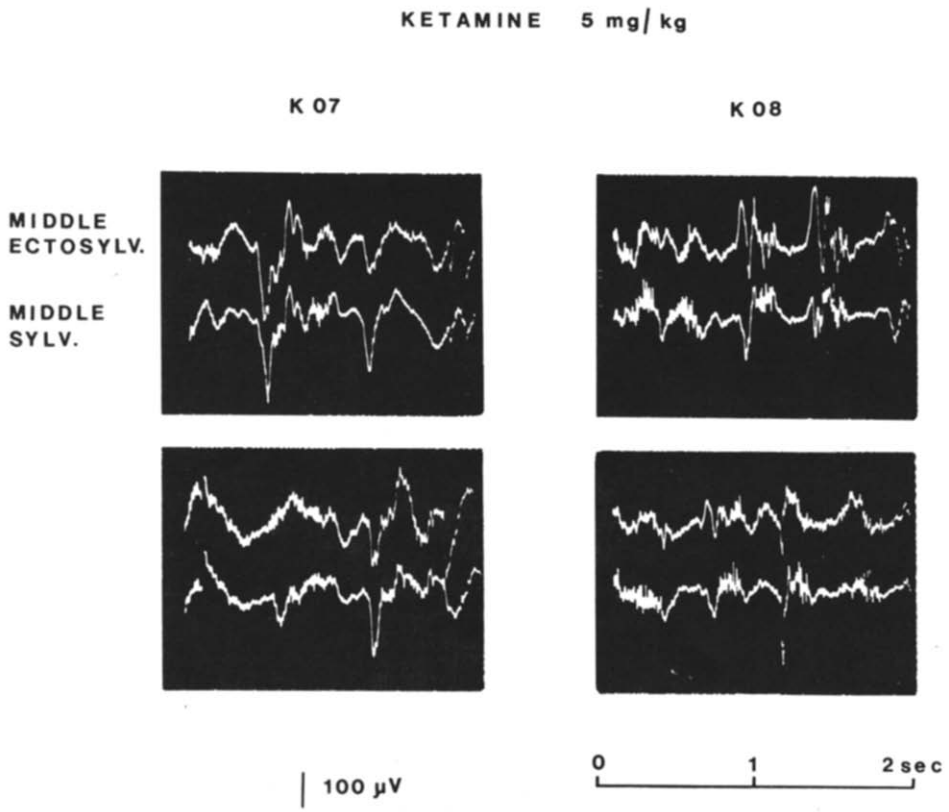

Fig. 3. Oscilloscopic tracing of electrocorticogram in 2 cats under Ketamine anesthesia. Unipolar recording reference to the bone of the frontal sinus.

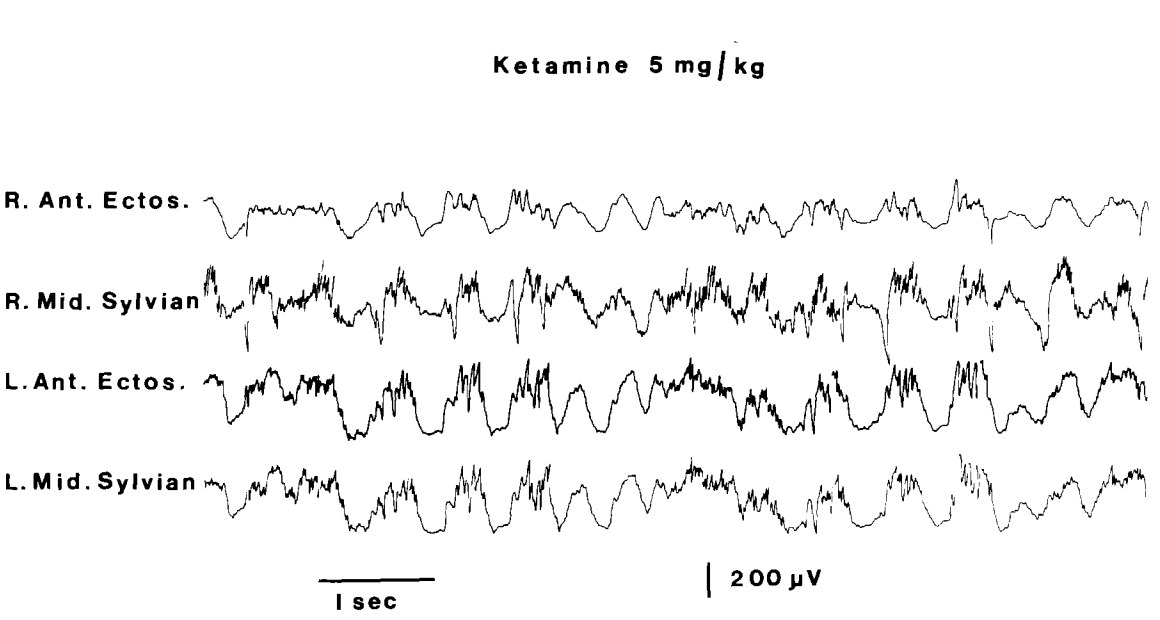

Fig. 4. Electrocorticogram during Ketamine anesthesia. Note that in this case Ketamine complexes are a mixture of delta waves and high voltage beta. Unipolar recording reference to the bone of the frontal sinus.

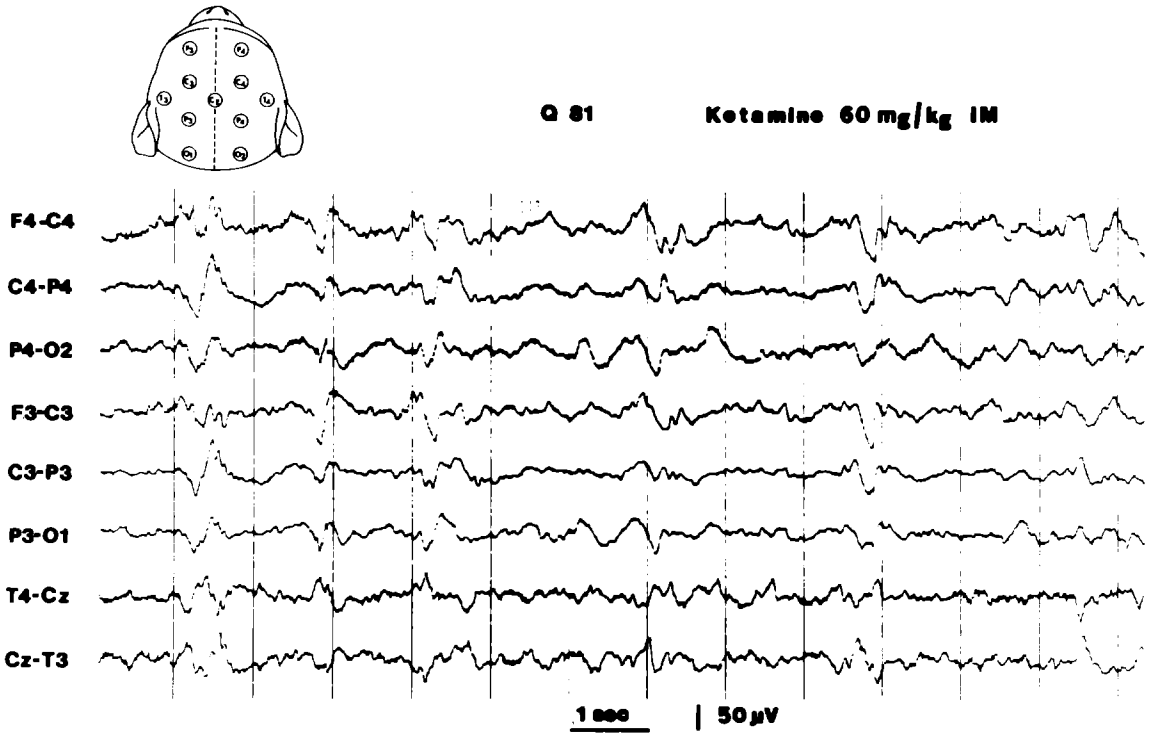

Fig. 5. EEG recording of monkey Q-81 during Ketamine anesthesia. Note the quasi-periodic occurrence of generalized bilaterally synchronous slow wave complexes. A terminology similar to the international 10–20 system is adopted.

Effect of Ketamine on focal epilepsy

The effects of Ketamine on penicillin epileptogenic foci were studied in 16 cats. In 8 animals penicillin foci were placed on the anterior sigmoid gyrus and in 8 animals on the middle ectosylvian gyrus. In 4 animals an additional penicillin focus was placed into the hippocampus. Epileptogenic activity was defined into two categories by electrographic criteria. Random occurrence of individual spikes or spike and wave complexes were termed "interictal epileptogenic activity". The occurrence of bursts of repetitive spikes in rapid sequence, usually followed by a brief period of postictal depression, was called "ictal activity" and was considered to represent an electrographic seizure. Interictal epileptogenic activity was obtained in all cases at the site of the injection (primary focus) and at the homologous contralateral cortical area (mirror focus). Electrographic seizures occurred in 6 cats.

Ketamine was injected intravenously after epileptogenic activity was well established. Three to four injections were administered to each cat at 1–1.5 h intervals. The first dose was usually 5 mg/kg. This was then followed by trials of 10, 15 and 20 mg/kg. The effects of these doses were similar, the only difference being the longer duration of the effect with higher doses.

Ketamine consistently suppressed focal seizures in the 6 cats where ictal activity was present (Fig. 6). Each animal received 3 trials of subsequent infusions. In each instance ictal activity was suppressed. Ketamine suppression lasted from 10 min to 2 h, the longest effects being caused by the higher doses. Ictal activity then spontaneously resumed.

Interictal epileptogenic activity was unaffected by Ketamine in 10 cases, transiently decreased (2–10 min) in 4 cases and moderately increased in 2 cases. In 3 of the 4 cats with decreased interictal activity, transient hypotension was noted following Ketamine injection (Fig. 7). Ketamine was always injected slowly and only a moderate depression of the blood pressure between 20 and 30 mm of mercury was observed in about two-thirds of the cats. In 2–3 min the blood pressure returned to pre-drug levels or

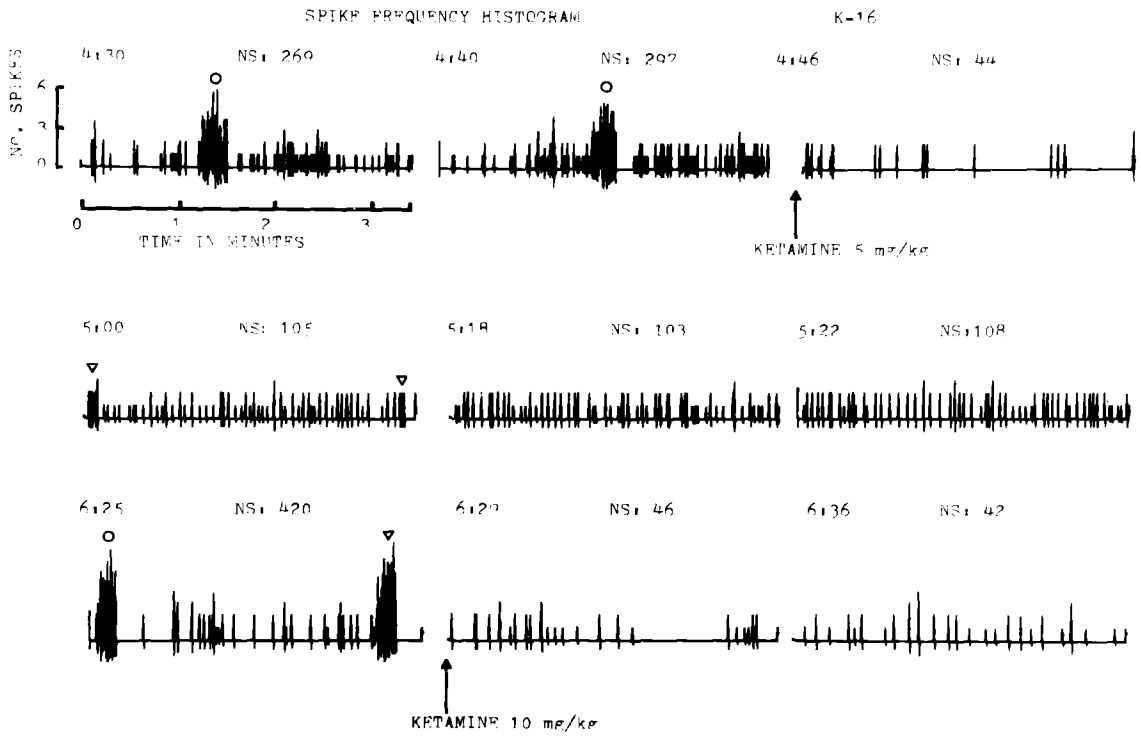

Fig. 6. Frequency histogram of penicillin spikes from the middle ectosylvian gyrus of cat K-16. Single bars represent interictal spikes. A cluster of bars fused together represents a focal seizure. Focal seizures marked with a circle are spontaneous seizures. Focal seizures marked with a triangle are second-induced seizures. The first number on the left above the histogram is the time in hours and minutes. NS is the number of spikes for a period of 3 min and 24 sec. Note that in this case Ketamine suppressed focal seizures and initially decreased the number of interictal spikes. 14 min later the frequency of interictal spikes had returned to normal. 1 h and 39 min later spontaneous and sound-induced seizures returned. A second administration of Ketamine had similar suppressing effects.

increased 20–30 mm higher than before the drug was given. Decreased ictal and interictal epileptogenic activity occurred both in cats with and without transient hypotension.

Expiratory CO_2 was monitored in 2 cats and ventilation was controlled to maintain them normocapnic. In both cases Ketamine 10 mg/kg did not modify the frequency of interictal epileptogenic activity. Additional Ketamine was administered in slowly incremental doses of 10 mg until a total of 145 mg/kg and 200 mg/kg respectively had been injected. In neither case was any change in the epileptic activity observed until 100 mg/kg had been injected; at that time interictal activity decreased. Additional Ketamine then suppressed interictal epileptogenic activity and depressed background activity. This was quickly followed by electrocerebral silence and death.

The effect of Ketamine was identical on primary and mirror neocortical and hippocampal epileptogenic foci (Fig. 7).

To ascertain the ability of our experimental model to develop focal seizure, Metrazol was used in 7 animals. Metrazol was injected intravenously in slowly incremental doses of 5 mg till either focal or generalized ictal epileptogenic activity was seen in the electrocorticogram. Usually 10–20 mg/kg of Metrazol were sufficient to activate focal seizures. In all 7 cats Metrazol activated the penicillin focus from the stage of rhythmic interictal spiking to the stage of focal ictal epileptogenic activity.

DISCUSSION

Our results showed that Ketamine initially

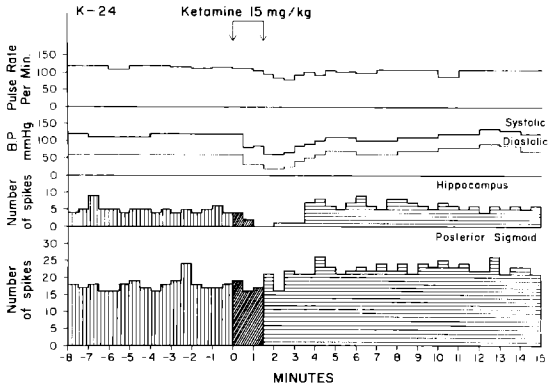

Fig. 7. Comparison of the effects of Ketamine on spike frequency, blood pressure and pulse rate. Ketamine injection was started at time 0 and was ended at 1.5 min. The firing of the neocortical penicillin focus (posterior sigmoid) was essentially unaffected by Ketamine. The hippocampal focus was depressed for 3.5 min. However, this depression is most likely due to the transient hypotension. As shown in this figure the drop in blood pressure preceded the diminution of hippocampal firing.

produced high voltage synchronous beta, then a mixture of generalized delta and beta and/or polyspike-slow wave complexes. Similar electrocorticographic findings have been reported by Miyasaka and Domino (1968), Mori *et al.* (1971) and Kayama and Iwama (1972). The dissociation of electrical activity between limbic and neocortical systems described by Corssen *et al.* (1968) was not confirmed in our study. We recorded identical, though asynchronous activity in limbic and neocortical structures. More *et al.* (1971), Kayama and Iwana (1972) and Winters *et al.* (1972) reported a similar lack of dissociation between neocortical and rhinencephalic systems and interpreted their findings as evidence that Ketamine induced electrographic seizures without clinical correlates. Mori *et al.* (1971) thought that Ketamine produced various degrees of CNS excitation culminating in "non-convulsive generalized electrographic seizures". These statements are based on the assumption that electrocorticographic spikes are synonymous of epileptic activity. Winters *et al.* (1972) refer to Ketamine complexes as "seizure discharges". Kayama and Iwama (1972) went a step further. They described the occurrence of synchronous slow waves in neocortical and subcortical nuclei and concluded that: "such generalized synchronism is most pertinent to the generalized seizures". We are reluctant to accept these conclusions for many reasons. As pointed out in the results it was often difficult to determine the true morphological nature of KCs. It was not always certain that the electrocorticographic changes produced by Ketamine were polyspike-slow wave complexes rather than a mixture of delta and high voltage beta. In a survey of the parameters of epileptic spikes we have shown (Celesia and Chen, in preparation) that the morphological appearance of a transient is not a sufficient criterion to identify spikes; furthermore spikes and beta activity have similar durations. The EEG, after all, is a "narrow band process" and waves of different physiological significance may have similar appearance. Elul (1972) emphasized this fact stating that the EEGs "do not exhibit sufficient variability of deflection patterns". Even if we accept that high doses of Ketamine induce generalized polyspike-slow wave complexes in the cat's brain, it does not necessarily signify that these complexes are epileptogenic. Not all spikes are manifestations of epileptogenic processes. Lambda waves, vertex sharp waves, PGO waves (Jouvet 1965) are examples of spikes representing normal physiological events.

Similarly synchronization of EEG rhythms is not exclusively epileptic. For example, EEG synchronization is observed in sleep spindles, paroxysmal theta during drowsiness and theta–delta build up during hyperventilation. This synchronization reflects physiological events often not even associated with CNS stimulation.

The theory of Ketamine inducing anesthesia by excessive stimulation of CNS is untenable when we observe the EEG changes it induces in monkeys and men. In both species Ketamine induces generalized high voltage synchronous beta and theta followed by the appearance at higher doses and/or deeper levels of anesthesia, of quasi-periodic delta complexes (Bennett *et al* 1973; Celesia *et al.* 1974). Bennett *et al.* (1973) first pointed out the similarity between these quasi-periodic complexes and the periodic EEG events seen in deep anesthesia and severe hypoxia, conditions usually associated with CNS depression. They further noted the similarity of these complexes with the periodic EEG changes of subacute sclerosing panencephalitis

(SSPE). Celesia (1973) studied the pathophysiology of SSPE complexes and concluded that they represent cortical events triggered by subcortical structures. The periodicity of these complexes as well as the periodicity of EEG transients seen in premature brain, deep anesthesia and cerebral anoxia was viewed as signifying a profound disruption of normal physiological processes both cortical and subcortical. Which specific subcortical systems were involved could not be determined. This same explanation may explain the effects of Ketamine.

Winters' (1972) hypothesis that the anesthetic state induced by Ketamine is due to "limbic seizures" is based exclusively on the morphology of brain waves. We must once again emphasize that this morphological approach may no longer be sufficient to differentiate between the states of central nervous depression and excitation nor in determining the boundary between physiological excitation and pathological excitation, the latter usually considered a manifestation of epilepsy. To untie this gordian knot we suggest the use of experimental models of epilepsy and the comparison of the drug under study with the effects of classic epileptogenic agents. We applied this method in the present work. Penicillin epileptogenic foci in the cat neocortex and hippocampus were unaffected by Ketamine and focal seizures were suppressed. The effects of Ketamine were compared to Metrazol which in every case activated both focal and generalized seizures.

Ketamine had no convulsant properties, but rather a mild antiepileptic effect. While the occasional depression of interictal epileptogenic activity may have been related to hypotension, the ictal suppression occurred both in normotensive and normocapnic cats: therefore, excluding the influence of hypotension and blood CO_2 changes as determining factors.

The reports of Bennett *et al.* (1973) and Ferrer-Allado *et al.* (1973) on the possible tendency of Ketamine to precipitate seizures have now been challenged by the well controlled studies of Celesia *et al.* (1974) and Corssen *et al.* (1974). These authors have administered Ketamine to 21 and 25 epileptic patients respectively without precipitating epileptic attacks. It is concluded that Ketamine has both depressant and excitatory properties and affects the central nervous system at many levels in different ways disrupting normal cortical and subcortical physiological activities.

SUMMARY

The effects of intravenously administered Ketamine were studied in 28 cats and 6 monkeys. In cats, Ketamine initially induced generalized high voltage beta activity followed by generalized slow waves. These slow waves were called Ketamine complexes (KCs) and had two different morphological appearances suggestive either of polyspike-slow wave complexes or of delta waves intermixed with beta activity. Often it was morphologically uncertain if KCs represented spikes-slow waves or a combination of beta-delta waves. In monkeys, Ketamine induced theta and beta rhythms and at higher doses, quasi-periodic slow wave complexes.

The effect of Ketamine on neocortical and hippocampal epileptogenic foci was studied in 16 cats. Ketamine consistently suppressed focal seizures but was ineffective in modifying interictal epileptogenic activity both at the primary and mirror focus. It was concluded that Ketamine had no epileptogenic properties. Ketamine affects the central nervous system at many levels in different ways. It simultaneously excites and depresses different systems and disrupts normal cortical and subcortical physiological activities.

RESUME

EFFETS DE LA KETAMINE SUR L'ACTIVITE EEG DU CHAT ET DU SINGE

Les effets de la Kétamine injectée par voie intra-veineuse ont été étudiés sur 28 chats et 6 singes. Chez le chat, la Kétamine provoque tout d'abord une activité bêta généralisée de haut voltage suivie par des ondes lentes généralisées. Ces ondes lentes ont été appelées complexes Kétamine (KCs) et ont deux aspects morphologiques différents évoquant soit des complexes de poly-pointe-ondes soit des ondes delta intriquées d'activité bêta. On peut souvent se demander du point de vue morphologique si ces KCs représentent des pointe-ondes ou une combinaison d'ondes bêta et delta. Chez le singe, la Kétamine provoque des rythmes thêta et bêta

et, à plus forte dose, des complexes d'ondes lentes quasi-périodiques.

Les effets de la Kétamine sur les foyers épileptogènes néocorticaux et hypocampiques ont été étudiés chez 16 chats. La Kétamine supprime de façon constante les crises focales, mais ne modifie pas l'activité épileptogène intercritique au niveau du foyer primaire ou foyer en miroir. Les auteurs concluent que la Kétamine n'a pas de propriété épileptogène. La Kétamine affecte le système nerveux central à plusieurs niveaux et de différentes manières. Elle excite et déprime simultanément différents systèmes et perturbe les activités physiologiques normales et sous-corticales.

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