Anesthesiology
57:451–457, 1982

The Tetraphasic Action of Lidocaine on CNS Electrical Activity and Behavior in Cats

Norimasa Seo, M.D.,* Eiji Oshima, M.D.,† John Stevens, M.B., F.F.A.R.C.S.,‡ Kenjiro Mori, M.D.§

Effects of intravenously administered lidocaine on CNS electrical activities were studied in cats with surface and depth electrodes implanted chronically in the brain. Lidocaine was administered using a constant rate infusion pump. The changes induced in CNS electrical activities were correlated with the behavioral changes in the unrestrained freely moving state. During infusion of lidocaine at the rate of 1 $mg \cdot kg^{-1} \cdot min^{-1}$, a sequence of changes was observed: the initial stage was represented by diffuse EEG slowing and a decrease of reticular neuronal firing, associated with behavioral depression; the second stage by low-voltage fast-wave EEG and increase of reticular neuronal firing, associated with agitation and/or catatonic behavior; the third stage by reappearance of slow-wave EEG and decrease of reticular neuronal firing, associated with a behavioral depression; and the fourth stage by an epileptiform EEG and increase of reticular neuronal firing associated with generalized tonic or tonic/clonic convulsions. Higher rates of infusion, such as 4, 8, and 15 $mg \cdot kg^{-1} \cdot min^{-1}$, diminished the manifestation of the signs of both electrographic and behavioral depression, leaving the signs of excitation unaffected or somewhat enhanced. These findings support the widely prevailing view that recording the surface EEG is not valuable diagnostically in detecting the onset of local anesthetic intoxication, in that the preconvulsive CNS state can be represented by either a high-voltage slow-wave or low-voltage fast-wave pattern in the surface EEG. (Key words: Anesthetics, local: lidocaine. Brain: amygdala; convulsions; EEG; hippocampus; reticular multi-unit activity; seizures. Complications: convulsions. Toxicity: convulsions.)

INTRAVENOUS ADMINISTRATION of a large dose of local anesthetic is believed to stimulate the CNS and induce generalized electrographic and behavioral convulsions in both humans and laboratory animals. However, the nature of the action of subconvulsive doses remains obscure. A review of the literature revealed that the signs and symptoms of intoxication by subconvulsive doses are a mixture of expressions of CNS excitation and depression[1–4]: symptoms and signs such as drowsiness or temporary unconsciousness are considered evidence of depression, while muscular twitching or tremor and epileptiform EEG of amygdala are forms of stimulation. Furthermore, contrasting views have been reported with regard to EEG findings in the preconvulsive state in experimental animals. Wagman *et al.*[5,6] reported that the initial change in the EEG with lidocaine intoxication was noticed only in the epileptiform activity of the amygdala and that the cortical EEG was relatively unaffected, while Munson *et al.*[7] reported diffuse slowing of the cortical EEG in the pre-seizure state. This discrepancy can be attributed to either the difference in species of animals or different methods of drug administration: Wagman *et al.* used cats and rabbits and administered the drug by bolus injection, and Munson *et al.* used rhesus monkeys and administered drugs using a constant rate infusion pump, thus elevating the blood level of the drug more slowly. The present study attempts to correlate the behavioral changes with those of CNS electrical activities, and also to resolve the previously reported discrepancy in the EEG findings during subconvulsive intoxication by lidocaine. For this purpose a relatively slow rate of infusion was used. The effects of different rates of infusion also were assessed.

Materials and Methods

Eleven adult cats of either sex, weighing 3.2–3.8 kg, were used for the experiments. Three weeks prior to the study, the cats were anesthetized with 40 mg/kg intraperitoneal pentobarbital and electrodes were implanted in the anterior suprasylvian gyrus, medial amygdala (A 12; L 9; H −6), dorsal hippocampus (A 2; L 8; H +8) and midbrain reticular formation (A 3; L 3 H −1) according to the atlas of Snider and Niemer.[8] The electrode positions were verified with 70-μm sections prepared with a freezing microtome after the experiments. EKG electrodes were placed subdermally on the chest. The cortical surface electrodes were made of stainless steel screws of 2.0-mm diameter, and were drilled so as to reach the dura. The reference electrode was placed in the frontal bone. The subcortical electrodes were side-by-side stainless steel wires, 0.2 mm in diameter, insulated wih epoxylite resin (except for the cut end), and the tips had a 0.5- to 1.0-mm vertical separation. The same wire was used for the EKG recording. All leads were soldered to a miniature vacuum

* Chief of Service, Intensive Care Unit, Kobe Municipal Central Hospital.
† Assistant of Anesthesiology, Kyoto University Hospital.
‡ Visiting Research Fellow, Kyoto University Faculty of Medicine.
§ Professor of Anesthesiology, Kyoto University Hospital.

Received from the Department of Anesthesiology, Kyoto University Hospital, Sakyo-ku, Kyoto 606, Japan. Accepted for publication May 10, 1982. Supported by Grant-in-Aid for Co-operative Research, No. 537023, from the Ministry of Education, Science and Culture, Japan, Intractable Disease Division, Public Health Bureau, the Ministry of Health and Welfare, Japan and Niwa Medical Research Foundation. Dr. Stevens was supported by a Japan Society for Promotion of Science/Royal Society Joint Fellowship. Presented in part at the 22nd Annual Congress of the Japan Society of Anesthesiology, Kansai District, October 2, 1976 (Jpn J Anesth 26:1070, 1977).

Address reprint requests to Dr. Mori: Department of Anesthesiology, Kyoto University Hospital, Sakyo-ku, Kyoto 606, Japan.

0003-3022/82/1200/0451 $01.15

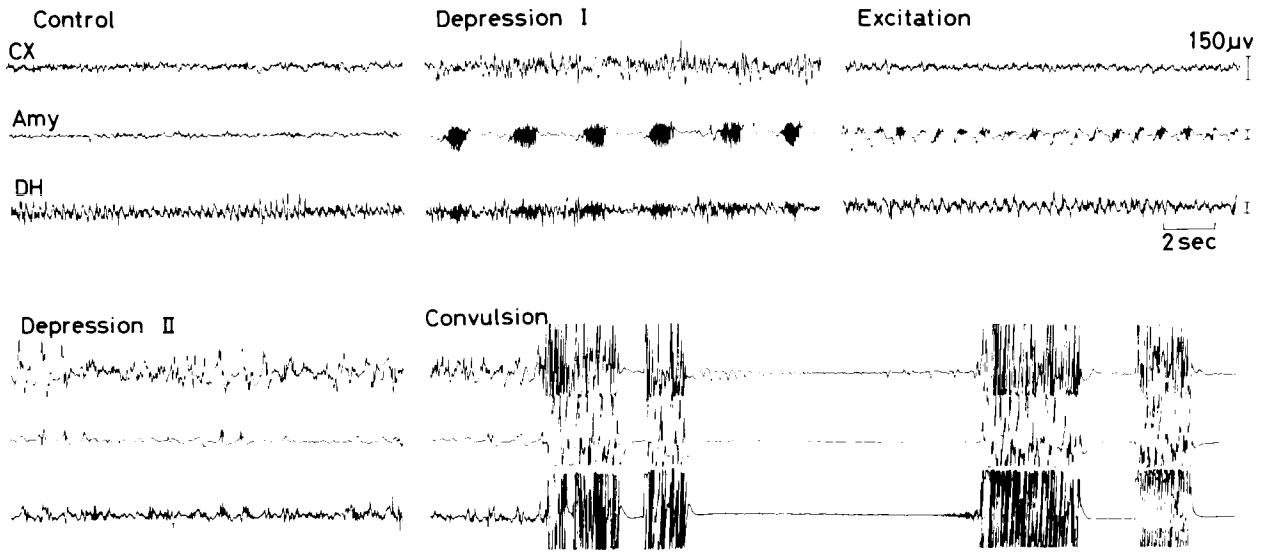

FIG. 1. EEG changes induced by intravenous infusion of 1 $mg \cdot kg^{-1} \cdot min^{-1}$ lidocaine. CX: anterior suprasylvian gyrus; Amy: nucleus amygdalae medialis; DH: formatio hippocampalis dorsalis; Depression I: the stage of initial depression; Excitation: the stage of excitation; Depression II: the stage of late depression; Convulsion: the stage of convulsion. For details, see text.

tube socket that was fixed to the skull with dental cement. During the experiment, the socket was connected to the recording devices with a bundle of flexible cables, 1.5 m long, in order to allow free movement in the observation box. EEG activities were recorded from the cortical and limbic structures, and multi-unit activity was recorded from the midbrain reticular formation. An eight-channel polygraph (Multi-purpose Polygraph, RM 85®, Nihonkoden Co., Tokyo) and a slow ink-writing oscillograph (Rectigraph 8s®, Sanei Co., Tokyo) were used to record the electrical activities. The methods of recording and measurement of multi-unit activity were described elsewhere.[9,10]

On the day of the drug study, the cat initially was anesthetized with halothane, 3% in oxygen, by insufflation in a small anesthesia box. A polyethylene cannula, 0.4 mm in external diameter, was inserted into the inferior vena cava through the femoral vein with the aid of a 16-gauge Argyle Medicut®. The catheter was fixed to the body with adhesive tape and the remaining venous line to the bundle of recording cables. Two hours later, when full recovery from anesthesia was confirmed by CNS electrical activities and behavioral observations, lidocaine was administered through the venous cannula by means of a constant-rate infusion pump until behavioral and electrographic seizures appeared. During the infusion of lidocaine, observations were made to correlate the behavioral changes with those of electrical activities.

The effects of infusion at the rate of 1 $mg \cdot kg^{-1} \cdot min^{-1}$ were observed in all cats and data were collected from eight, in which movement artefacts did not disturb the evaluation of CNS electrical activity. In two cats, the effects of different rates of infusion, 4, 8, and 15 $mg \cdot kg^{-1} \cdot min^{-1}$, were compared. Each infusion rate was assessed in different experimental sessions at 7-day intervals. The recovery phase was compared in these two cats with the infusion phase, and for different infusion rates. In each experiment, the level of reticular multi-unit activity and heart rate obtained while the cat was standing quietly served as a control, and the changes were expressed as per cent changes of control value at different CNS states induced by lidocaine infusion. Statistical significance of changes was determined by Student's t test for paired data when $P < 0.01$.

Results

Typical examples of changes in the EEG pattern and reticular multi-unit activity are shown in figures 1 and 2. Continuous infusion of lidocaine, 1 $mg \cdot kg^{-1} \cdot min^{-1}$, induced distinct tetraphasic action in both behavioral and electrographic criteria.

The Stage of Initial Depression

The cats that were standing or walking initially were stretched out on their abdomens with their forelegs extended, hindlegs flexed, chins placed on the floor, and eyes open. The control EEGs of cortical low-voltage fast waves and hippocampal theta waves were both replaced by irregular high-voltage slow waves. The characteristic spindle-like activity appeared in the amygdaloid nucleus in synchrony with respiration. The reticular multi-unit

activity was progressively depressed by 19 ± 4% of control level of wakefulness (mean ± SEM) ($P < 0.001$).

The Stage of Excitation

The cat suddenly lifted its head, extended its forelegs but kept its hindlegs flexed, and vocalized violently and repeatedly. Respiration became rapid and panting in nature. The pupils were maximally dilated and urination, defecation, and/or vomiting occurred frequently. The reticular multi-unit activity increased rapidly and was greater than the level of control wakefulness by 54 ± 13% ($P < 0.001$ when compared with the values of both control and the initial depression). The cortical EEG showed low-voltage fast waves. The spindle-like activity of the amygdaloid EEG persisted, but the frequency increased in parallel to the increase in the respiratory rate. The cats did not respond behaviorally or electrographically to external stimulations such as probing of the body with a rod.

The Stage of Late Depression

The cats entered into this stage gradually. The cats vocalized less frequently and less violently, swung their heads occasionally, but usually remained quiet in a similar posture to that seen in the initial stage of depression. The eyes were open but the cats did not respond to probing of the body. The EEG pattern was again represented by an irregular high-voltage slow-wave pattern. The amygdaloid spindle-like activity disappeared and was replaced by irregular slow waves and spikes. The amygdaloid spikes were sporadic initially and then appeared repeatedly and synchronously in other leads at

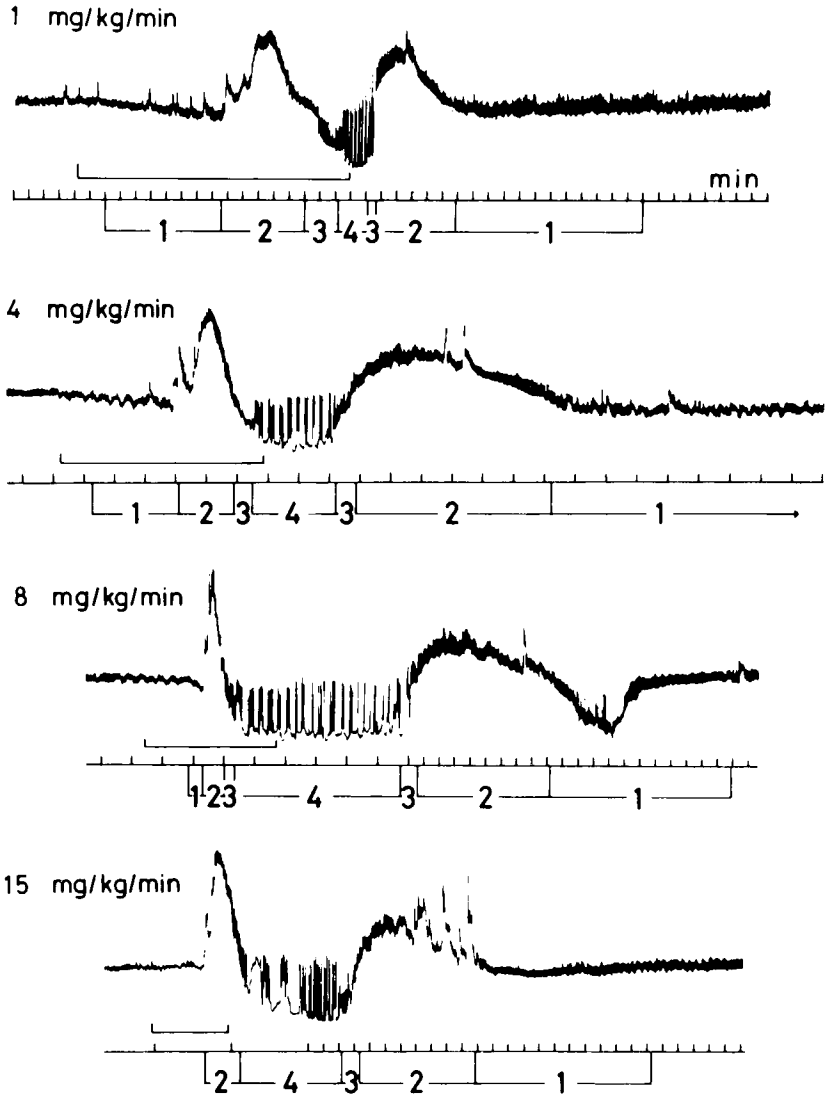

FIG. 2. Effects of different rates of infusion on the reticular multi-unit activity. There was an interruption of 7 days between each experiment. Each trace represents the average integrated multi-unit firing of a population of neurons in the midbrain reticular formation. The time scale line also represents the system noise level which was obtained by inserting 10-kΩ resistor across the input in place of the ainmal. Changes in the level of neuronal unit firing are measured as the distance from the multi-unit tracing to the 10-kΩ resistor line: the upward shift of the tracing shows the increase in the firing rate of units and the downward shift shows the decrease. Bracketed areas indicate the period of infusion of lidocaine. As the changes occurred more rapidly in higher infusion rates, faster paper speeds were used to demonstrate the infusion period more clearly, but as changes during recovery occurred more slowly, the paper was slowed for the latter part of the experiment to condense the trace. The arabic numbers written below the time scale line indicate the stages of lidocaine effects: 1 = the stage of initial depression; 2 = the stage of excitation; 3 = the stage of late depression; 4 = the stage of convulsion. Note that during infusion of 15 mg · kg^{-1} · min^{-1}, the stages of initial and late depression are absent during the infusion period, while they can be noticed during the recovery period. For details, see text.

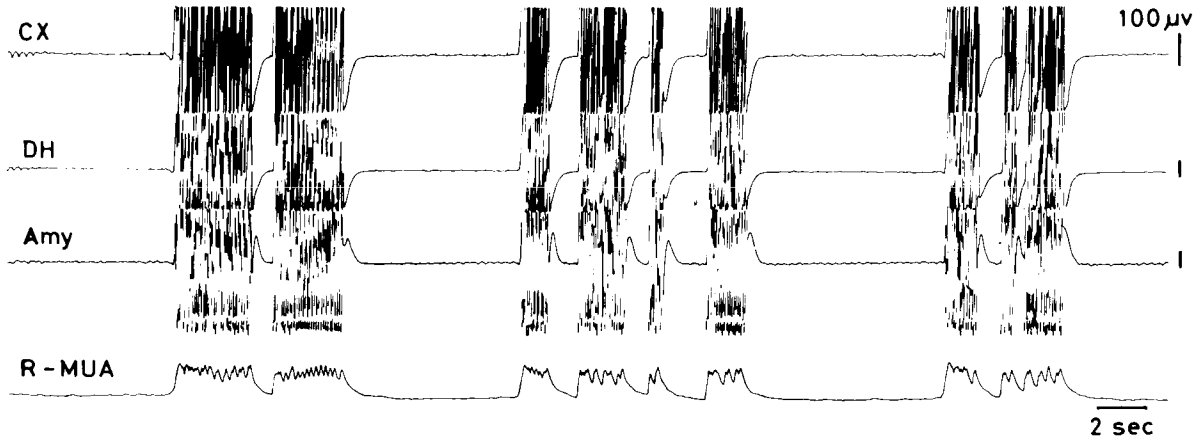

FIG. 3. EEG and reticular multi-unit activity in status epilepticus induced by lidocaine infusion. R-MUA = average integrated reticular multi-unit activity. Other abbreviations are the same as those in figure 1. Note that the EEG epileptic discharges are associated with marked increases of the reticular neuronal firing and the inter-ictal EEG quiescence with its decrease.

end of this stage. The reticular multi-unit activity was depressed gradually to a level less than control by 39 ± 5% ($P < 0.001$).

The Stage of Convulsion

This stage began suddenly following quiet behavior. No prodromal signs, such as twitching of extremities or whiskers, could be seen by observation. The cats suddenly extended all four limbs, and went into a lateral position. The eyes were widely open and the pupils maximally dilated. The convulsion was mostly tonic, lasting 4–8 s, and interrupted by quiescent periods of 2- to 8-s duration (figs. 1, 3, and 4). The convulsion and the succeeding quiescence could be induced repeatedly when lidocaine infusion was continued. During convulsions, the EEG showed high-voltage high-frequency spikes in all recorded areas, and during the succeeding inter-ictal quiescent period there was electrical silence. The reticular multi-unit activity showed large fluctuations, the ictal EEG being associated with an increase to a level greater than control by 2 ± 8% of control, and the inter-ictal EEG quiescence with a decrease to a level less than control by 66 ± 4%. Both the increase from the pre-ictal level to that during convulsion and the decrease from the convulsive level to the inter-ictal level were statistically significant ($P < 0.001$), while the difference between control wakefulness and the ictal level was not significant statistically.

The cumulative doses of lidocaine were 10.3 ± 0.6 mg/kg at the stage of excitation, and 24.8 ± 2.5 mg/kg for the induction of convulsions. During lidocaine infusion, the pulse rate showed a biphasic response from a control rate of 158 ± 6 min^{-1} (mean ± SEM). A decrease of 16 ± 6% of control ($P < 0.001$ when compared with control) was seen at the end of the stage of initial depression, 21 ± 2% ($P < 0.001$) at the maximum excitation stage, and 34 ± 2% ($P < 0.001$) at the end of

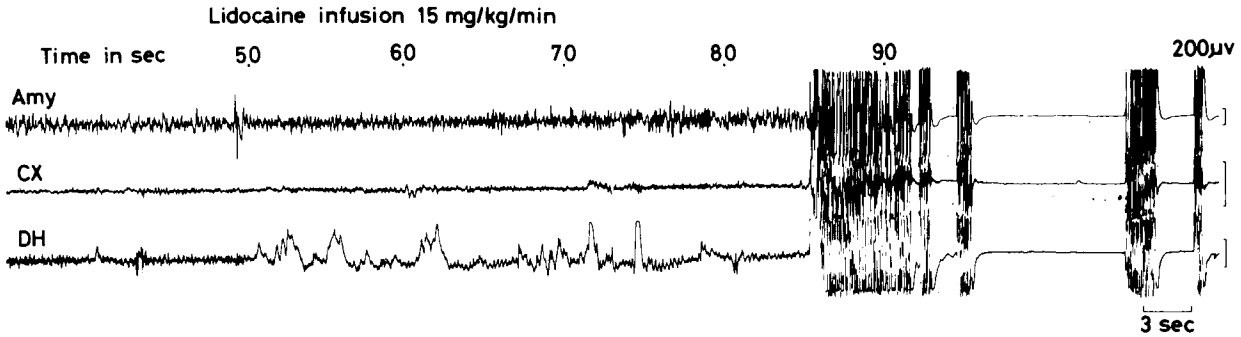

FIG. 4. EEG changes induced by intravenous infusion of 15 $mg \cdot kg^{-1} \cdot min^{-1}$ lidocaine. Abbreviations are the same as those in figure 1. The numbers written above the EEG records indicate the time in seconds after the initiation of lidocaine infusion. Note that the cortical EEG does not change until the sudden appearance of epileptic discharges, while spindle-like activity is noticed in the amygdala from 70 s of infusion. The large fluctuations in the hippocampal lead are movement artefacts.

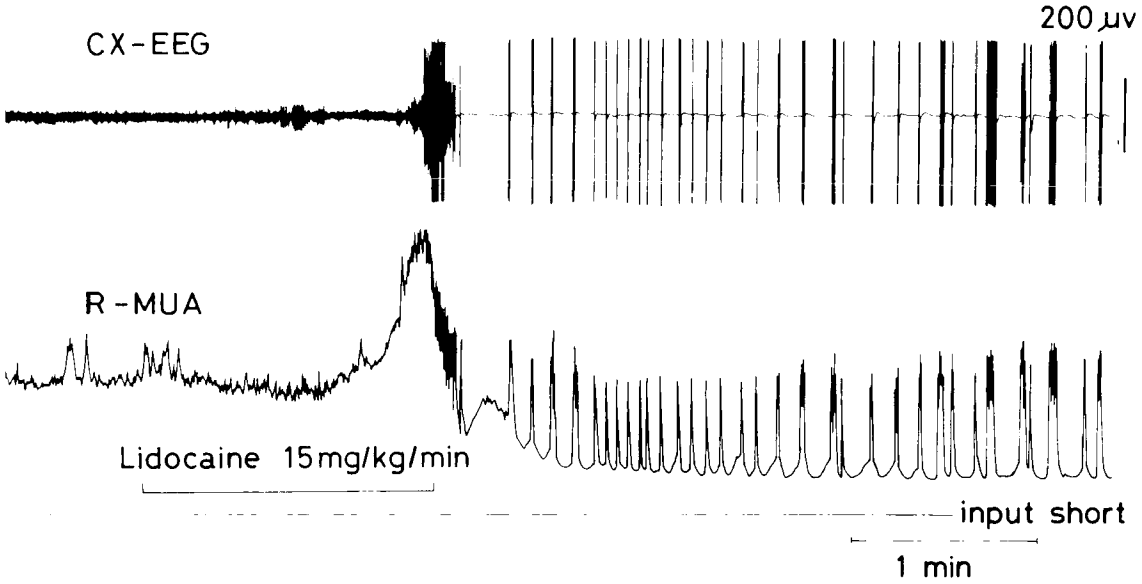

FIG. 5. Effects of lidocaine infusion, 15 mg·kg·min^{-1}, on the reticular multi-unit activity and cortical EEG. This record was taken from the same experiment as figure 4. R-MUA = average integrated reticular multi-unit activity. In this case, the generalized seizure occurred at the maximum activation of the reticular multi-unit activity. For details, see the text.

the late depression stage. This was followed by a slight recovery to a level which was still less than the control by 27 ± 4% ($P < 0.001$) during the convulsions.

When higher doses per unit time of lidocaine were administered, the previously described behavioral and electrographic sequence of events occurred more rapidly, and the CNS electrical activities associated with behavioral depression, at both initial and late stages, became less evident, while those associated with behavioral excitation were left unaffected or even somewhat exaggerated. During infusion of 4 or 8 mg·kg^{-1}·min^{-1}, although behavioral signs of depression were not evident, the EEG slowing and the decrease of reticular multi-unit activity could be confirmed during both initial and late stages of depression. Furthermore, in both cats, the higher the dose per unit time of lidocaine, the less the decrease of reticular multi-unit activity, the decrease being minimal when the infusion rate of 15 mg·kg^{-1}·min^{-1} was used. In contrast, the higher the dose per unit time of lidocaine, the greater the degree of increase of reticular multi-unit activity at the stage of excitation, and the maximum increase was seen at the infusion rate of 15 mg·kg^{-1}·min^{-1}, which was greater than during 1 mg·kg^{-1}·min^{-1} by approximately 35% in one cat (fig. 2) and by 28% in another cat. When lidocaine was infused at the rate of 15 mg·kg^{-1}·min^{-1}, the EEG seizure began at the maximum level of increase of reticular multi-unit activity in one cat (fig. 5) and during falling phase from the peak of increase in another cat. In both cats, the EEG seizures were preceded by the amygdala spindle-like activity. However, the cortical EEG showed only a low-voltage fast-wave pattern similar to that of control wakefulness and the generalized seizure began suddenly (figs. 4 and 5).

Once a generalized seizure occurred, the differences in dose per unit time did not alter the behavioral and electrographic manifestations. The maximum level of increase in reticular multi-unit activity during ictal phase and its level during inter-ictal quiescence did not vary with different doses per unit time of lidocaine, and the severity of convulsion appeared similar on visual inspection. During recovery from the stage of convulsion, the correlation between behavioral criteria and electrographic findings observed during infusion could not be reproduced. When the infusion of lidocaine was discontinued, the stage of convulsion continued for a certain period of time, and the cat then became quiet. The reticular multi-unit activity showed three definite stages, decreased, increased, and again decreased activity, and then returned to the control level of wakefulness (fig. 2). However, the EEG showed high-voltage slow waves not only during the stages of decreased activity but also during the stage of increased activity (fig. 6). Furthermore, there was no spindle-like activity in the amygdaloid EEG; the cats were essentially quiet, did not vocalize, and showed no behavioral signs of CNS excitation.

Discussion

It is generally considered that in humans, recording the surface EEG is not useful in detecting the onset of local anesthetic intoxication prior to convulsions.[3,4] This has been based on the findings that the early subjective

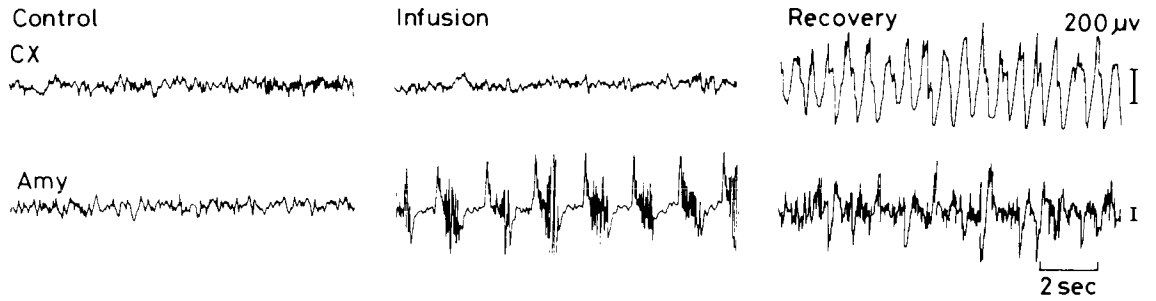

FIG. 6. Comparison of the EEG pattern of lidocaine-induced CNS stimulation during the infusion period and recovery. Abbreviations are the same as those in figure 1. Note that during the infusion period, the control EEG is characterized by low-voltage fast waves similar to that of control, and that of the amygdala by the spindle-like activity, while during recovery period, the cortical and amygdala EEGs both show high-amplitude slow waves, and the amygdala spindle-like activity cannot be seen.

and objective symptoms and signs of intoxication in humans, such as light headedness, dizziness, drowsiness, etc., are not noticeably reflected in the EEG except for some shift from the pattern of wakefulness to that of light sleep.[3] Using a constant-rate infusion technique and a slower rate of infusion than were used by other workers, we found a definite tetraphasic sequence of changes in the CNS electrical and behavioral activity. The initial EEG slowing and depression of reticular multi-unit activity, coupled with a less-active behavior, indicated that the initial sign of intoxication was characterized by apparent CNS depression. The succeeding low-voltage fast-wave EEG and increase in reticular neuronal firing, associated with agitation and/or catatonic behavior indicated, at least to some extent, activation of the CNS. The reappearance of a high-voltage slow-wave EEG and a decrease in the reticular neuronal firing, coupled with some behavioral depression again indicated apparent depression of the CNS. The final stage was represented by an epileptiform EEG associated with an increase in reticular neuronal firing and behavioral convulsion. The recovery phase from the convulsion stage was represented by a reversal of the sequence of changes in the reticular neuronal firing: there was a return to the control level following stages of decreased, increased and again decreased activity. However, these changes during recovery were not accompanied by changes in the EEG or behavior. The dissociation of reticular neuronal activity, the EEG, and behavior can not be definitely explained by results of the present study, but it may possibly be a post-ictal phenomenon resulting from exhaustion. Of particular interest was the fact that although the reticular neuronal firing definitely was enhanced during seizures, the degree of enhancement did not significantly exceed the control level of wakefulness and that the maximum stimulation by lidocaine was induced not with the convulsive dose but rather with a subconvulsive dose.

The present study showed that a slow rate of infusion of lidocaine induced both diffuse slowing and activation of EEG patterns, while a rapid rate of drug infusion masked the components of CNS depression and induced only activation of the CNS electrical activities, as noticed in the case of bolus injections of the drug by Wagman *et al.*[5,6] Their studies did not detect activation of the surface EEG prior to the appearance of seizures, possibly because the EEG pattern of activation is similar to that of wakefulness and is difficult to differentiate. This was seen with drug administration at a rate of 15 $mg \cdot kg^{-1} \cdot min^{-1}$ in the present study.

The tetraphasic action of lidocaine, as seen in the present study, does not appear to have been documented by previous investigators. Munson *et al.*[7] in their study in rhesus monkeys mentioned only the diffuse slowing of the cortical EEG as a pre-convulsive CNS effect; however, their figures show a high-voltage slow-wave EEG (corresponding to the stage of initial depression) at 3 min, a low-voltage fast-wave EEG (stage of excitation) at 4 min, a high-voltage slow-wave EEG (stage of late depression) at 5 min, and succeeding generalized epileptiform EEGs (stage of convulsion) during intravenous infusion at the rate of 4 $mg \cdot kg^{-1} \cdot min^{-1}$ (See figure 1 of Munson *et al.*[7]). The time course of this sequence of events was identical to that found in the present study. The findings of Wagman *et al.*,[5,6] who observed no pre-ictal EEG changes in the surface recording following bolus injection of convulsive doses of lidocaine in cats, were also reproduced in the present study by rapid infusion of lidocaine in the same species of animal. These findings together indicate that the previous discrepancy in the pre-convulsive EEG findings between Wagman's and Munson's groups can be attributed not to the difference of species of animals used but rather to the difference of rate of administration.

Intoxication by local anesthetics in clinical practice usually occurs when a large intravascular injection is

given by mistake or when repeated local infiltrations are performed. Although direct extrapolation of the findings obtained in laboratory animals to humans is not valid, the present study indicates that not only the diffuse slowing of surface EEG but an EEG pattern very similar to that of wakefulness represent the pre-convulsive CNS stage in lidocaine intoxication. Therefore, it is also our belief that recording the surface EEG is not of diagnostic value in detecting the onset of local anesthetic intoxication.

The authors thank M. Ohara at Kyushu University for assistance in preparing the manuscript.

References

1. Ritchie JM, Greene NM: Local anesthetics. The Pharmacological Basis of Therapeutics. Edited by Gilman AG, Goodman LS, Gilman A. New York, Macmillan, 1980, pp 300–320
2. Covino BG, Vassallo HG: Local Anesthetics. New York, Grune & Stratton, 1976, pp 123–130
3. de Jong RH: Local Anesthetics. Second Edition. Springfield, Charles C Thomas, 1977, pp 84–114
4. Steen PA, Michenfelder JD: Neurotoxicity of anesthetics. ANESTHESIOLOGY 50:437–453, 1979
5. Wagman IH, de Jong RH, Prince DA: Effects of lidocaine on the central nervous system. ANESTHESIOLOGY 28:155–172, 1967
6. Wagman IH, de Jong RH, Prince DA: Effects of lidocaine on spontaneous cortical and subcortical electrical activity: Production of seizure discharges. Arch Neurol 18:277–290, 1968
7. Munson ES, Martucci RW, Wagman IH: Bupivacaine and lignocaine induced seizures in rhesus monkeys. Br J Anaesth 44:1025–1029, 1972
8. Snider RS, Niemer WT: A Stereotaxic Atlas of the Cat Brain. Chicago, University of Chicago Press, 1961
9. Mori K, Kawamata M, Mitani H, Yamazaki Y, Fujita M: A neurophysiologic study of ketamine anesthesia in the cat. ANESTHESIOLOGY 35:373–383, 1971
10. Mori K, Winters WD: Neural background of sleep and anesthesia. Int Anesthesiol Clin 13:67–108, 1975