Effects of Lidocaine on the Central Nervous System

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It is well known that local anesthetics, which block impulses in peripheral nerve fibers, have marked effects on central nervous system function. These drugs, when given intravenously in small doses, produce anticonvulsive or anesthetic effects,1, 5, 6, 7, 19, 21, 24, 28, 44, 49 and in higher dosage produce convulsions.1, 5, 6, 10, 18, 23, 24, 31, 52 As anesthetics, they exhibit similarities but many differences in comparison with general anesthetics.

We undertook a systematic investigation of the central effects of lidocaine, in order to obtain data which would have bearing upon the mechanism of action of local anesthetics. We began with a study of the changes in spontaneous electrical activity which occur at cortical and subcortical levels in alert, normal cats and in rabbits with chronically implanted electrodes.57, 58 Concomitant studies on acute preparations were done to evaluate the influence of physiological factors such as blood pressure and PaCO₂ on the response to lidocaine.12, 54 Experiments were also performed to evaluate the effect of the drug upon evoked activity in the brain.46, 59

Simultaneous behavioral and electrical observations were made on cats and rabbits with electrodes chronically implanted by means of stereotaxic techniques. Electrodes were placed within representative structures in limbic, specific, and association-sensory areas, ascending reticular system, and in non-specific thalamic nuclei. For reasons soon apparent, the olfactory bulb was implanted in several cats in order to monitor respiratory rate.42, 43 In some animals, respirations were recorded by means of a fine thermocouple inserted into a nostril.

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Results

Effects of Subconvulsive Doses

Behavioral Effects. The effects of a rapid intravenous injection of lidocaine were similar in both cats and rabbits, although each species differed in sensitivity to the drug. In the rabbit, the threshold dose necessary to produce a seizure was as low as 5–6 mg./kg., while in the cat a comparable dose ranged from 10–12.5 mg./kg. Within 30 seconds to 1 minute after injection, a sub-convulsive dose produced marked depression of motor activity in the form of a decrease in spontaneous movement and loss of tone, more striking in the cat than in the rabbit. Depression of motor activity lasted 4–5 minutes, during which there was a markedly reduced response to pressure on the paw, pinching the limb, or loud noise. We could not tell whether these effects were the result either of a motor effect or to an alteration of sensation, or both. The pupils dilated transiently but returned to normal size within one minute. Respiratory tidal volume decreased, but the respiration rate either slightly increased or was not affected. The cat gave a hoarse cry and the rabbit a brief squeal im-
mediately following the injection. Urination and defecation occurred on occasion, responses more usual with higher subconvulsive doses.

It was our impression that lidocaine produced a change in the state of consciousness. The animals stared and were less alert following injection, but they never appeared asleep. The eyes remained open, and sleep postures were not assumed. Depression of motor activity and decreased response to stimuli could have been due, at least in part, to sedation.

Acute experiments showed that the potential in the mid-brain reticular formation evoked upon sciatic nerve stimulation was depressed after lidocaine, and that the course of depression was often comparable to the duration of the behavioral changes. Figure 1 illustrates these results as well as a less marked effect on the evoked potential in the somatosensory cortex.

**Electrical Effects.** The most striking and consistent electrical change produced by a subconvulsive dose of lidocaine was seen in the amygdala. This change took several forms: a rhythmic high voltage discharge; similar high-voltage discharge with a brief high-frequency burst superimposed on one of the limbs; or, a rhythmic spindle burst (figs. 2 and 3). The amygdaloid spindling (fig. 2A, 2 min. trace and 2B) sometimes occurred abruptly without previous electrical change, especially after low doses of lidocaine; spindles appeared 10–25 seconds after injection and lasted for two minutes or longer, frequency within each spindle was from 14 to 16 per second, and the spindle burst frequency ranged between 40 and 180 per minute (rate higher in the rabbit than in the cat). This activity gradually subsided over one to five minutes. Spindling, synchronous with the amygdaloid discharge but of much lower voltage, was sometimes seen in fronto-orbital cortex, n. medialis dorsalis, mid-brain reticular formation, globus pallidus, putamen, and hippocampus. None of the other structures studied in these experiments showed the spindle response at any time. Wagman et al., in preparation, lists in detail the structure studied.

With higher subconvulsive doses of lidocaine, the other amygdaloid changes noted above preceded the spindling. Figure 3 illus-
Effects of a Convulsive Dose

Behavioral Effects. The seizure produced by a rapid intravenous injection of lidocaine was quite distinctive and similar for both cat and rabbit. In no instance were similar behavioral or electrographic changes produced by intravenous injection of saline or inadvertent sub-
cutaneous injection of lidocaine. The seizure began within 10 to 15 seconds after injection with a tonic extension of limbs and head followed by a few clonic jerks of limbs and head; duration was usually 10 to 20 seconds, although on some occasions, up to 60 seconds. In most instances, other behavioral changes preceded the motor attack: fast, shallow respiration, pupillary dilatation, vocalization, arrested movement, sniffing in the rabbits, sometimes defecation and/or urination. At times a seizure was accompanied by marked excitement and agitation and patterned behavior such as clawing at the air or hissing. The electrographic concomitants consisted of rhythmic focal amygdaloid spike-spindle or spike discharge. Clonic motor activity was associated with bursts of high voltage but more generalized spike activity, seen in the depths and on the surface. Subsequent clonic jerks were also associated with more generalized electrographic bursts of rapid high voltage spiking. A sequence seen in many animals suggested that a focal discharge could begin in the amygdala and become generalized to other depth structures, and could occur with little or no abnormality on the surface.

Following a seizure the changes resembled those seen after a subconvulsive dose as described above: marked depression of spontaneous motor activity, alteration in posture and a reduction in responsiveness to stimuli. After about 5 minutes the animal appeared normal.

Electrical Effects. A commonly observed sequence of electrical events after a convulsive dose of lidocaine is illustrated in figure 5. Ten seconds after injection, a focal discharge, incremental in voltage, consisting of rhythmic spike-like potentials, developed in the basal

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Fig. 3. Effects of relatively higher but still subconvulsive dose of lidocaine in cat with chronically implanted electrodes. Illustration in detail of sequential changes in four different parts of the amygdala, in hippocampus, and in cortex. Details in text. Occluding nostrils had same effect on spindling as it did on rhythmic spike activity illustrated here at 4 minutes. Ab(ant), anterior portion of basal amygdala; Ab(post), posterior portion basal amygdala; Acl, lateral portion central amygdaloid nucleus; Hipp, hippocampus; So, anterior sylvian gyrus; Ps, posterior sylvian gyrus.
Amygdala, later seen in other leads especially the lateral amygdala and olfactory bulb. Arrested movement and staring occurred during electrical discharge. The amygdaloid discharge culminated in high voltage generalized seizure activity in all leads including the surface (not shown in Fig. 5). The generalized activity was accompanied by clonic jerks of head and limbs. Following the termination of generalized activity, the changes noted were similar in all respects to those seen during a subconvulsive dose. Similar activity of much lower voltage also occurred in putamen, globus pallidus and reticular formation.

We were particularly interested in the fact that postictal suppression of amygdaloid activity was seen in only one animal, a rabbit. In this experiment a generalized seizure pro-
duced by lidocaine was followed by a flattening in all leads except for the basal amygdala, which showed prominent focal spiking. Following this focal discharge a postictal flattening which lasted about 1 minute was seen in the amygdaloid trace. At this time rhythmic spiking was present in the other regions. Nine minutes after injection the most prominent fea-

Fig. 5. Effect of rapidly administered convulsant dose of lidocaine in an alert cat with chronically implanted electrodes. Description in text. Put, putamen; Al, lateral amygdaloid nucleus; GP, globus pallidus; Ab, basal amygdaloid nucleus; MRF, mesencephalic reticular formation; OB, olfactory bulb.
Pa CO₂ = 35 mm Hg

L. Ant

R. Acc

L. F-S

L. S-Vis

LIDOCAINE - 10 mg/kg

Fig. 6. Effect of rapid administration of lidocaine in acutely prepared, immobilized cat, artificially respirated at rate of 24/min. through tracheal cannula with tidal volume to maintain PaCO₂ at 35 mm. Hg. Spiking in anterior amygdala lasted 9½ minutes, not dependent on respiration. Spiking seen on cortex (at 9 minutes) was infrequent occurrence. Ault, anterior porition basal amygdala; Acc, central amygdaloid nucleus; F, S, and Vis, frontal, suprasylvian and visual cortical surface placements. No further localization possible because of needle electrode placements in skull.

The electrical seizure did not always begin in the amygdala. Where large convulsive doses were given, the discharge appeared almost simultaneously on the surface and in the depths.

The Effect of CO₂ on Lidocaine Produced Seizures

Two striking changes in spontaneous electrical activity took place after sedative or convulsive doses of I.V. lidocaine. One, the cortical slowing; the other, the sequence of events in the amygdaloid nuclear complex. We believe that the latter, together with the associ-
ated behavioral changes indicate an excitatory action of lidocaine on the amygdala. Further studies on acute preparations supported the hypothesis derived from the data in the implanted animals, that lidocaine has a direct excitatory effect on the amygdala independent of its effects upon respiration (see discussion). Acute experiments also revealed that changes in $P_{\text{CO}_2}$ had a marked influence on the effects produced by lidocaine.

The acute experiments were performed on cats initially anesthetized with halothane, immobilized with flaxedil and artificially respired. Cortical and depth recordings were made from the same loci as in the chronic animals. In addition, blood pressure and $P_{\text{CO}_2}$ were continuously recorded on either a Grass model 5 or 7 polygraph or an Offner Dynograph R, the former parameter measured by means of a statim transducer, and the latter by means of a Beckman LB-1 infrared analyzer. Our final analyses were based on $P_{\text{CO}_2}$ measured in blood samples withdrawn immediately prior to each injection of lidocaine.

The animals were respired with tidal volumes producing a $P_{\text{CO}_2}$ between 30 and 36 mm. of mercury with oxygen added to maintain an inspired concentration of 23 to 24 per cent as measured by a Beckman Oxygen Analyzer, Model B. $P_{\text{CO}_2}$ was varied by adding $CO_2$ to the inspired mixture, delivered from calibrated flowmeters to a reservoir bag connected to the inspiratory side of a respirator; stabilization of $CO_2$ occurred within 20 minutes.

Two to four intravenous injections of lidocaine were given in each experiment; after one injection, another was not given until spontaneous electrical activity had returned to the pre-injection pattern and blood pressure and $P_{\text{CO}_2}$ had stabilized.

The effects of lidocaine were not necessarily dependent upon nasal air flow (fig. 6) for the drug produced a focal epileptiform discharge in the amygdala in an animal mechanically ventilated through a tracheal cannula. Spiking occurred in the anterior amygdala after 35 seconds, maximal at nine minutes and terminated at 9½ minutes. Spindle bursts were never seen in the amygdala, although in a few cases abortive spindles were recorded in the hippocampus and prepyriform cortex. As in the implanted chronic animals, lidocaine invariably produced cortical slowing regardless of spiking or abortive spindles in the depth loci under observation. Cortical slowing outlasted amygdaloid spiking (fig. 6).

Generalized “seizures” were produced. These were defined as paroxysmal bursts of high voltage spikes in both depth and cortical leads, lasting 1 to 5 seconds, with relatively quiet periods between bursts. They were similar to the discharges accompanying the behavioral seizures produced by the higher lidocaine doses in the chronically implanted animal. Onset of seizures was usually 8 to 12 seconds, although occasionally more delayed, and associated with transient arterial hypotension and a flattening of the EEG. Duration varied from 15 seconds to several minutes. At times lidocaine produced a 1/sec. high voltage spiking in the cortical leads, occurring either irregularly or spaced in groups of about 5 seconds duration. Lower voltage faster cortical activity continued between these periods of spiking. In the analysis of our results we entered this “intermediate” pattern in the “no-seizure” group. Following the seizure, cortical slowing was produced and often lasted for several minutes.

$P_{\text{CO}_2}$, lidocaine dosage, and hypotension may be important variables relative to the production of seizures. Hypotension as a crucial factor was eliminated in the following manner. When systolic blood pressure was plotted against time of onset and duration of each seizure for every trial, we found that in any one experiment a seizure might occur at either a lower or a higher blood pressure than that at which no seizure occurred. Thus blood pressure bore no apparent relationship to the onset, duration or occurrence of seizures. (The initial cortical flattening, however, did seem to be related to the transient hypotension.)

The two parameters related to the occurrence of seizures were found to be the dose of lidocaine and the $P_{\text{CO}_2}$. Within the limits of $P_{\text{CO}_2}$ employed (15-93 mm. Hg) the higher the arterial $P_{\text{CO}_2}$ the lower was the dose of
Fig. 7. Activation by subconvulsive dose of lidocaine of focal discharge in R.A.med. and L. Hipp in chronically implanted rabbit which, as result of a freeze lesion had previously developed a spike focus in L. Hipp and R. Hipp, followed later by a focus in R.A.med. Respiration was recorded by means of a nasal thermocouple. Control records A and B, low-voltage, sharp, epileptiform discharge (usual state for this animal at this time) can be seen in L. and R. Hipp, and in R.A.med. About 95 seconds after an injection of 5 mg./kg. lidocaine, prominent focal spiking seen in R.A.med. At 135 seconds, built up to a rhythmic discharge; later (260 seconds), also seen clearly in R. Hipp. No correlation between spike activity and respiratory frequency or amplitude. Note that epileptiform discharge in depths and the surface slowing are blocked by arousal (noise at 260 seconds). Activation of focal spike discharge did not ordinarily occur with sleep and cortical slowing. A.med, medial portion of central amygdala; Aud, auditory cortex, surface. Hipp, hippocampus; cc, corpus callosum; M. Mes, medial motor cortex; AM, N. anterior medialis of thalamus; Limb, limbic-cortex surface.
lidoceaine required to produce a seizure. Englesson et al.20 have recently confirmed these results in dogs.

Effects of Subconvulsive Doses Upon Evoked Potentials

Lidoceaine in subconvulsive doses significantly alters several classes of evoked responses.66 Although blockade of conduction in small fibers may contribute to these alterations13 the effects may also be due to disturbances in synaptic function produced by lidoceaine. The data may be summarized as follows:

(1) Rather than uniformly affecting all components of an evoked response, the drug appeared to selectively affect later components while sparing early positivities (fig. 1).

(2) In some cases evoked alterations in recovery cycles occurred with stimulus intervals as long as 200 msec.

(3) Changes in the latencies of evoked responses which might be expected if fiber conduction were permanently affected, were not seen after lidoceaine injection.

(4) In systems, in which effects upon conduction in fibers as opposed to synaptic activity could be compared, only the latter were markedly affected. For example, responses in the optic tract at the geniculate level to chiasmal stimulation were unaffected in latency or amplitude by doses of lidoceaine which blocked the later negativities of the cortical responses evoked by the same stimulus.

(5) Changes in evoked potentials could not be correlated with alterations in blood pressure, cortical steady potentials or $P_{a_{co2}}$.

Discussion

Effects of Lidoceaine on the Limbic System

Local Electrical Effects. The most striking changes in spontaneous electrical activity after "sedative" or convulsive doses of lidoceaine took place within the amygadaloid nuclear complex. With large doses the same alterations in spontaneous activity were seen in synaptically related distant structures (e.g., MD, fronto-orbital cortex, hippocampus) and in adjacent nuclei (globus pallidus and putamen). The focal nature of these changes requires explana-

tion. In low doses, lidoceaine accentuated the normal respiratory dependent spindle activity in the amygadala. It might be argued that the changes in amygadaloid activity were the result of alterations in respiratory rate and volume rather than a specific effect of the drug on the amygadala. Spindle bursts in the amygadala, dependent upon nasal air flow, are well known 22,17,26 and may be affected by drugs that alter respiration.17

However, several observations make the above interpretation unlikely. While the results shown in figures 3 and 4 merely show the dependence upon nasal air flow of spindles induced by subconvulsant doses, the discharges seen with convulsive doses may be independent of respiration. It was also shown in acute experiments (fig. 6) that focal discharge (but not spindling) occurred in the amygadala after lidoceaine in intubated animals and in animals with tracheal cannulae. Gault and Coustan,27 showed that either cocaine or lidoceaine increased spindling in the olfactory bulb and in artificially ventilated animals supplied with rhythmic nasal air flow. However, in our chronic preparations, there was poor correspondence between respiratory volume and spindle size. Pentyletenetrazole, even though producing hyperpnea, did not induce spindles or spike-spindle complexes in the amygadala comparable to those of lidoceaine. It would appear then that effects upon respiration alone are insufficient to explain the focal changes in amygadaloid activity after lidoceaine.

There was a dose dependent continuum of electrical and behavioral alterations produced by lidoceaine and with a high enough dosage seizures occurred, often accompanied by focal amygadaloid discharge. It was not clear at which point on this continuum the behavioral and electrical seizures began. Appearance of spike-like discharges or a combination of spikes and slow waves synchronous with respiration caused by higher doses of lidoceaine has not been described by others who studied amygadaloid activity in a variety of natural and drug-induced states.17,26,31,35a,39 It is possible that the rhythmic spiking seen in figure 3, though synchronous with respiration, represents a form of ictal activity, "triggered" by efferent volleys from the olfactory system.
Possible Mechanisms of Action. Many of the behavioral and electrographic observations can be explained by the hypothesis that lidocaine in addition to its diffuse effects, has an excitatory action upon the amygdaloid nuclear complex. The focal amygdaloid discharges coincided closely with the onset of behavioral changes. The behavioral changes correspond to those reported as resulting from direct electrical stimulation of the amygdala,29, 55, 57, 60, 53 and to those in animals with "amygdaloid epilepsy." 22, 59 The finding that epileptogenic foci in the amygdala may be activated by lidocaine (Prince and Wagman, personal communication) provides further evidence for this hypothesis (fig. 7).

Although no attempt was made to map the pathways of spread of amygdaloid-seizure activity after lidocaine, the distribution of such activity in the hippocampus, medialis dorsalis, mid-brain, and basal ganglia was similar to that found in studies of propagation of amygdaloid seizures, by Arna-Isigquez et al.2 Both the amygdaloid seizures initiated by electrical stimulation and those caused by lidocaine often remain localized to subcortical structures without reflection on the surface.

Excitatory effects upon the amygdala might be due to the removal of a normally afferent inhibitory influence, as reasoned by Preston 45 to explain the effects of chlorpromazine which produces both tranquilization and increased activity of the amygdala. In this context it is important to recall that a local anesthetic can block conduction in small peripheral nerve fibers without affecting conduction in the larger. Such an effect possibly could account for differential blocking in the central nervous system.

There is evidence that lidocaine affects the release of noradrenaline from isolated nerve granules;21 raising the possibility that lidocaine has an effect upon a synaptic mediator selectively present in the amygdala. The high serotonin content of the cat's amygdala 8 may be of importance in this connection.

The postulated excitatory effects of lidocaine cannot easily be reconciled with its known action as a membrane stabilizer, which would decrease the sensitivity of change in sodium conductance upon depolarization 11, 48 and decrease the efflux of K from cortex. 10

Tanaka and Yamasaki suggested, on the basis of extracellular unitary data, that lidocaine selectively blocks inhibitory synapses of cortical neurones. 54 Intracellular recordings (Prince, personal communication) have not confirmed these findings. The known blocking action of local anesthetics is still to be reconciled with their excitatory action on some central nervous system mechanisms.

Effects of Lidocaine on Other Areas of CNS

Slow Cortical Activity. There are several possible explanations for the cortical slowing produced by lidocaine: (1) slow waves result from hyperventilation and hypocapnea; (2) slowing is secondary to hypotension; (3) pontical activity; or (4) a type of slowing which normally would accompany drowsiness and sleep. Since slow activity was also seen in acute preparations in which the P<sub>co2</sub> was stabilized, it cannot be entirely dependent upon hyperventilation. Furthermore, as noted above, in the normal animal lidocaine did not invariably produce hyperventilation. Hypotension as an explanation can be dismissed because in acute preparations slowing was either not associated with hypotension or else greatly outlasted a small (15-20 per cent) transient fall in systolic blood pressure. Pontical activity is unlikely because surface slowing frequently occurred without preceding seizure activity. The fourth possibility listed seems the most likely explanation. An alerting stimulus could convert slow surface activity to low voltage fast activity, suggesting that slowing resembles that seen in "natural" sleep, or sleep induced by small doses of sedatives such as pentobarbital. This interpretation is further supported by the accompanying behavioral changes during which the animal was for a time less responsive.

Other Possible Mechanisms. It is difficult to ascribe the observed behavioral changes to drug action at any one site. In addition to local effects on amygdaloid activity, I.V. lidocaine may alter conduction in peripheral nerve, 13 or may block evoked responses and interfere with portions of peripherally and centrally evoked cortical responses (fig. 1). The relaxation and decreased responsiveness noted
above are most likely the composite result of actions of lidocaine at several levels.

That EEG slowing began some time after the onset of behavioral changes suggests that alteration in cortical function is not primarily responsible for the apparent "sedation." French et al.\textsuperscript{31} also noted that the "depressed state" of monkeys after I.V. procaine was not always reflected in a hypersynchronous EEG. Cortical slow activity and sedation might be related to a partial transient deafferentation as suggested by Hodes.\textsuperscript{55, 53} Studies on man confirm the impression that lidocaine has a distinct sedative effect.\textsuperscript{52, 58}

**Factors Possibly Modifying the Effects of Lidocaine**

**Dosage and Species Difference.** The dose of lidocaine is important in determining the variety and sequence of electrical and behavioral changes. Since they begin within one circulation time, speed of injection and concentration of drug are important variables. We have mentioned the differences between cat and rabbit in terms of drug dosage. Recent personal observations suggest that the response is further different in the rhesus monkey.

**Alterations in Blood Pressure.** In the present experiments and those of Prince et al.,\textsuperscript{45} there was no correlation between alterations in blood pressure and the development of seizures with convulsant doses, or blockade of evoked potentials with sub-convulsant doses of lidocaine.

**Anesthetics.** The influence of other anesthetic drugs on the effect of lidocaine may be important in determining values for the convulsive dose of the local anesthetic. In artificially respirated dogs, anesthetized with pentobarbital, deKornfeld and Steinhaus\textsuperscript{11} failed to produce seizures with doses up to 60 mg./kg. administered over 30 minutes. On the other hand, Acheson et al.\textsuperscript{1} produced seizures in artificially respirated cats breathing nitrous oxide and oxygen with doses as low as 10 mg./kg., somewhat lower than our threshold seizure dose. Acheson et al. used a mask to administer the gases, thus conceivably increased dead space and inspired CO\textsubscript{2} concentration.

**The Effect of Carbon Dioxide.** We have shown, that the higher the PaCO\textsubscript{2} up to 100 mm. of mercury, the lower the threshold dose of lidocaine needed to produce a seizure. Fink and Schoolman\textsuperscript{22} found that normal PaCO\textsubscript{2} of the cat is 27.2 ± 3.4 mm. of mercury, a value, if lower than that of the rabbit, might explain the difference noted between these species.

Two possible explanations for the effects of CO\textsubscript{2} are: (1) increased PaCO\textsubscript{2} can result in lidocaine reaching the brain more rapidly and in greater concentration; (2) carbon-dioxide per se may have an excitatory effect on limbic structures, especially on the amygdala.

The most plausible explanation for the action of CO\textsubscript{2} is through an increase in cerebral blood flow. Reivich\textsuperscript{47} has shown that in the range of PaCO\textsubscript{2} that we used (20-90 mm. of mercury) there is a nearly linear relation between PaCO\textsubscript{2} and log CBF. We believe the effects of CO\textsubscript{2} in increasing permeability of the blood-brain barrier and altering the dissociation of lidocaine by changes in pH, play a minor role in the responses to lidocaine.\textsuperscript{12}

Carbon dioxide also exerts an influence on excitability of the neocortex and subcortical structures. Recent experiments in which arterial pH and PmCO\textsubscript{2} were independently manipulated demonstrated that PaCO\textsubscript{2} is an important determinant of cortical excitability.\textsuperscript{52, 60, 61} Moderate increase in PaCO\textsubscript{2} depresses excitability of the neocortex. On the other hand there is evidence to indicate that CO\textsubscript{2} affects the brain stem oppositely to that of the cortex.\textsuperscript{5} Other studies suggest that increasing PmCO\textsubscript{2} excites brain stem reticular and hypothalamic areas while depressing cortical neuronal activity.\textsuperscript{15, 25, 50, 56} There is even less experimental evidence bearing upon effects of CO\textsubscript{2} on the amygdala. Maiti and Domino\textsuperscript{41} reported that withdrawal of an animal from high CO\textsubscript{2} concentrations (up to 35 per cent) produced excitation, probably representative of activity at lower concentrations of CO\textsubscript{2}. In their experiments high CO\textsubscript{2} concentrations initially produced hypersynchronous waves and spikes in the amygdala. It is possible that increased PmCO\textsubscript{2} produces increased excitability of the amygdala, which therefore would become more sensitive to the effects of lidocaine.
Summary

Intravenous lidocaine, administered rapidly to alert cats and rabbits with chronically implanted brain electrodes, produced a reproducible sequence of behavioral and electrical changes, including cortical slow activity and changes in the amygdaloid nuclear complex. The latter, most striking, were rhythmic, and occurred in a dose-related sequence. They usually began as rhythmic spindling, progressed to spike-spindle complexes, spiking, and finally to ictal episodes which may become generalized.

With low doses of lidocaine, rhythmic amygdaloid activity was synchronous with tidal air flow through the nostrils. With higher doses, the discharges may be independent of respiration, and often begin focally in the amygdala and may proceed to a generalized clonic seizure.

Studies of evoked potentials as well as the changes in cortical activity indicated that lidocaine has diffuse effects on the CNS. Nevertheless, the behavioral and electrical observations led to the conclusion that the drug has a more specific action; namely, an activating effect on the amygdaloid nuclear complex.

Several important factors may effect the threshold dosage of lidocaine necessary to produce a convulsion. These include animal species, other anesthetics, and transient hypotension. The latter, however, was shown to have no influence on the seizure threshold dose. Threshold was dependent upon the \( P_{\text{CO}_2} \), shown by acute experiments on artificially respirated cats. In the \( P_{\text{CO}_2} \) range between 20 and 100 mm. of mercury the higher the \( P_{\text{CO}_2} \) the lower was the dose of lidocaine needed to produce a generalized electrical seizure. Two mechanisms may be mainly responsible: (1) Increased \( P_{\text{CO}_2} \) increases cerebral blood flow, allowing more lidocaine to reach the brain and the amygdala, per unit time. (2) \( CO_2 \) in moderately high concentrations has a direct excitation effect on the amygdala, and perhaps on other limbic structures.

Most of the experiments were carried out at the Biomechanics Laboratory and Department of Anesthesia, University of California School of Medicine, San Francisco, and at the Stanford University School of Medicine.

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**Discussion**

Dr. Krnjevič: I would like to point out that the evidence for lidocaine's having a specific effect in blocking cortical inhibition is quite unsatisfactory.

Dr. Wagman: I agree that the evidence presented by Tanaka and Yamasaki is not convincing. Dr. Prince, using intracellular recordings, has not confirmed their findings.

Dr. Krnjevič: How soon after you change the Pco2 do you see an effect? During a change in Pco2, one often sees a large excitatory effect, but if it is stabilized at a high level, you might see depression.

Dr. Wagman: The answer to this involves our technique. In these experiments we never went above an arterial Pco2 of 90 mm. Hg. We continually monitored Pco2 by means of the Beckman infrared analyzer (Model No. LB-1), and we never injected lidocaine until Pco2 had been constant for at least half an hour. More important, perhaps, is the fact that almost all our data are based on Pco2. Immediately before each drug injection we took an arterial blood sample which was analyzed for Pco2 and Pco2.

Dr. Usubiaga: Dr. Wagman's presentation, clarifies work done by Dr. Sorel (Electr. Clin. Neurophys. 17: 473, 1964) pointing to the centrifugal origin of local anesthetic-induced seizures. Intravenously given local anesthetics is a common technique of general anesthesia in South America. For this reason, my associates and I have done some work on animals and man (Proc. IIIrd World Congress of Anesth. Sao Paulo 1: 225, 1964).

In man, behavioral and electroencephalographic
effects of intravenous lidocaine were somewhat different than in animals. Salivation and lacrimation diminished, swallowing and blinking decreased in frequency and nystagmus was seldom seen. Subjectively, the subjects reported tinnitus, vertigo, tingling of the fingers and warming of the skin. Muscle hypotonia was never observed. On the contrary, muscle hypertension and even rigidity appeared. Cutaneous reflexes such as the abdominal and corneal were diminished or abolished, whereas tendinous reflexes such as the Achilles were markedly enhanced. Furthermore, continuous clonus of the patella, lasting for several minutes, could be easily elicited.

Effects on the blood pressure were variable, whereas ventilation was always depressed. In most of the subjects, consciousness was lost before they convulsed. In two, memories of the preconvulsive and convulsive episodes were recalled. Lidocaine induced convulsions of the tonic-clonic type, in doses ranging from 6 to 9mg/kg, depending on the rate of administration. The duration of the convulsive episode lasted from 1 to 3 minutes. Recovery of consciousness was regained within 10 to 15 minutes, and 40 minutes after the convulsions, the subjects were able to sit up and dress unaided.

During the preconvulsive period, no characteristic changes in the EEG were observed. During the convulsion, two well differentiated phases were seen. Fast frequency (6-9 cycles per second) high voltage spikes (up to 500 microvolts) were associated with the tonic muscle contractions, whereas slow frequency spikes appeared during the clonic phase of the convulsion. After the seizure ceased, a flat EEG tracing was observed (fig. 1). Within a minute or so, delta waves appeared and after 10-20 minutes alpha activity became predominant. It was of interest that when seizures were terminated by the injection of thiopental, a fast EEG recording instead of the flat after-discharge tracing was observed. Suxcynylcholine injected during the seizure did not modify either the EEG convulsive tracing, or the after-discharge period. Obviously, suxcynylcholine stopped muscle contractions.

Dr. Calindo asked about the changes in Pco2 and pH on the passage of local anesthetics through the blood-brain barrier. We found in dogs that hypercapnia increases the passage of local anesthetics and its metabolites across the blood-brain barrier. The effects of CO2 were more marked than corresponding changes in pH. We also observed, as did Dr. Wagan, that hypercapnia lowers the threshold for local anesthetic-induced convulsions, and prolongs the duration of the seizures.

We do not wish to speculate on the mechanisms underlying these effects. We do not know whether local anesthetic-induced convulsions are produced by stimulation of the rhinencephalon or by depression of inhibitory pathways, as does strychnine. We do know, however, that procaine, lidocaine, or dibucaine injected into psychiatric patients that were to have electroshock-therapy, protected the brain against the electrical stimulation. We observed that local anesthetics not only increased the threshold for stimulation and decreased the duration of the tonic-clonic electrically induced seizures, but after the highest doses, they prevented the appearance of any generalized convulsion induced by the electrical current. This seems to indicate that local anesthetics are central nervous system depressants.

Dr. de Jong: I would like to discuss some of the central nervous system reactions to injection of lidocaine in patients with temporal lobe epilepsy.

Ever since the discovery of the local anesthetic properties of cocaine, systemic manifestations have been observed in man. Best known of these reactions are generalized tonic-clonic seizures, resembling grand-mal epilepsy. At lower local anesthetic blood levels, sedation, sleep, lack of responsiveness and a state resembling analgesia may be observed. Intravenous infusion of local anesthetics has found application in the treatment of pain, and as a supplement to general anesthesia. Little known in this country is the fascinating finding by Bernhard and Bohn (Bernhard, C. G., and Bohn, E.: Local Anaesthetics as Anioco-

![Fig. 1.](image-url)
well as sedative and excitant properties at intermediate dose levels.

Paroxysmal high voltage spike and spindle bursts in the cat's amygdala have been interpreted by us (Wagman, I. H., de Jong, R. H., and Prince, D. A.: Effects of lidocaine on spontaneous cortical and subcortical activity; production of seizure discharges. Submitted to Electroencephal. Clin. Neurophysiol.) as representing focal amygdaloid seizures. It has been pointed out by Eidelberg (Eidelberg, E., Neer, H. M., and Miller, M. K.: Anticonvulsant properties of some benzodiazepine derivatives: possible use against phychomotor seizures. Neurology 15: 223, 1965) that cocaine-induced amygdaloid seizures in cats and rats bear a strong resemblance both electrically and behaviorally to temporal lobe seizures in man. This author employed local anesthetic-induced amygdaloid seizures as a pharmacologic model for the testing of anticonvulsant drugs. The presence of hippocampal and amygdaloid seizure activity in temporal lobe epilepsy suggested to us that local anesthetics might induce a similar syndrome in man. The symptomatology of subconvulsant doses of local anesthetic, loss of attention, staring, chewing and swallowing movements, automatism, decreased auditory acuity, anxiety, dreamy state and fine extremitiy tremors, has several points of resemblance to the psychomotor seizure syndrome.

An unusual opportunity to test the action of lidocaine on the human hippocampus and amygdala was presented in a series of patients under investigation for refractory temporal lobe epilepsy at the University of California, San Francisco and Los Angeles Medical Centers. Some of the patients came from the group discussed earlier by Dr. Brazier. Eight patients were given intravenous lidocaine at a rate of 0.5–2.0 mg./kg./minute to a total dose of 4–10 mg./kg. Six patients developed a psychomotor seizure identical to their usual pattern, preceded by a visual or epigastric aura. Loss of hearing, automatism and decreased external contact were observed. Grand-mal seizures were avoided by terminating the injection of lidocaine with onset of the psychomotor seizure. Rather than arterial hypotension which we fully expected, systolic hypertension as high as 190 mm.

Fig. 2. Spontaneous electrical activity from temporal lobe electrodes during lidocaine-induced psychomotor seizure. Right and left temporal lobe recording bundles each contain 3 electrode pairs, separated by 1 cm. Inferior pair (tem. inf.) presumably is located in the amygdala. Spontaneous paroxysmal high voltage discharges coincident with a psychomotor seizure were earlier recorded from right amygdala leads in this patient. Note sudden appearance of high amplitude paroxysmal spikes grouped in bursts of 2–3 sec. duration in right inferior temporal leads (tracings 1, 4 and 7) following IV injection of 250 mg. lidocaine. Changes in other leads are minimal; some slowing and increased amplitude are evident. In tracing 4, one electrode is in amygdala, the other 3 cm. superior; tracing 7 leads from the same electrodes, but frequencies above 2 Hz. are filtered out to show slow activity. Bipolar records. R. and L. = right and left. Temp. = temporal lobe, inf. = inferior, mid. = middle, sup. = superior. Reproduced by permission from: de Jong, R. H. and Waits, L. F.: Lidocaine-induced psychomotor seizures in man. Acta Anaesth. Scand. Suppl. 23: 598, 1968.
of mercury was seen (fig. 2). Electrical seizure activity in man showed large amplitude paroxysmal spikes grouped in bursts, presumably arising from amygdala or hippocampus. Spike bursts usually were seen only unilaterally, and were quite circumscribed in location. Onset and duration of spike bursts, which resembled electrical activity during spontaneous seizures, were clearly correlated with the lidocaine-induced psychomotor seizure. The electrical and behavioral responses to lidocaine injection in man have a striking resemblance to the focal amygdaloid seizures seen in chronically implanted cats reported above.

Although projection to normal man is still speculative, the syndrome of a subconvulsive CNS reaction to local anesthetic has much in common with a petit-mal seizure. It is possible that in man too, lidocaine induces focal amygdaloid (or hippocampal) seizures at moderately high blood levels of the drug. This focal limbic seizure may well be the central determinant of many of the CNS manifestations of local anesthetic injection. At higher blood levels of local anesthetic, limbic centers are presumably excited first, with subsequent rapid spread of synchronous paroxysmal firing, grossly manifested as a grand-mal seizure.