Intracerebral Gas Anesthesia by Diffusion through Silicone Rubber

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The technique of diffusion of anesthetic gases and vapors through silicone rubber has been applied to the direct diffusion of these agents into the brain of the cat. A hypodermic needle with a Silastic membrane at its tip was inserted into the reticular formation. Light anesthesia was produced rapidly with a single injection of as little as 0.10 ml. of anesthetic gas or liquid into the needle shaft. The anesthetics produced their effect in a specific area of not more than 3–4 square millimeters in the brain. The potential uses of this technique in research and clinical anesthesia are discussed.

WE have reported that anesthetic gases and vapors can be admitted to the blood stream by diffusion through intravascular silicone rubber catheters or arteriovenous shunts.[1] We have also demonstrated the potential application of this new method to the administration of anesthetics and to the rapid determination of anesthetic depth.[2, 3]

In the present report we describe new findings based upon the property of rapid diffusion of anesthetics through Silastic. Minute volumes of anesthetic gas or vapor may enter the reticular formation of the brain by diffusion through a Silastic membrane at the tip of a hypodermic needle stereotaxically positioned in the midbrain of a cat. Anesthesia is induced rapidly. A method for the study of the effect of anesthetic activity on the brain is also outlined.

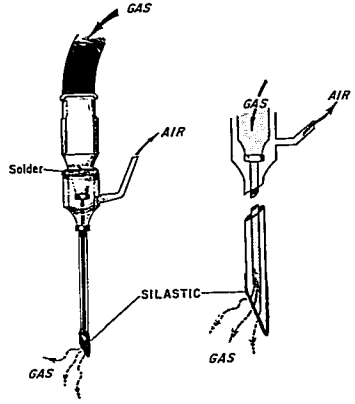

FIG. 1. Diagram of intracerebral chemode made from hypodermic needles.

Method

Preparation of the Silastic-Occluded Hypodermic Needle. A thin-wall #18 needle is shortened so that the needle shaft is 2.2 cm. long. The upper third of the hub is removed with a fine saw (fig. 1). The tip of the needle is occluded with a tiny drop of Silastic cement,[••] which is allowed to dry overnight so that a tough, thin Silastic membrane becomes bonded to the needle tip. A #23 hypodermic

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•• Extracorporeal and Medical Specialties Company, Inc., Mt. Laurel, N. J.

needle is shortened appropriately so that its tip will set just above the membrane and its hub will fit flush with the #18 hub when the smaller needle is inserted into the larger one. The needle hubs are soldered together. A hole is drilled in the side of the #18 hub and a short segment of another needle is inserted and soldered in place. This is an exhaust vent. After final assembly, saline or gas can be flushed into the hub of the #23 needle and will pass over the Silastic membrane and out of the exhaust vent. The total volume of the inner needle shaft is 0.10 ml.

Insertion of the Silastic-occluded Hypodermic Needle into the Brain

Fifteen cats weighing 2.5 to 3.5 kg. were used. The cats were anesthetized with pentobarbital and placed in the prone position. Using aseptic technique, a midline incision was made over the skull and a 3 mm. burr hole was made to one side of the midline. A tiny hole was made in the dura with a fine needle. The Silastic membrane tip of the needle was then positioned in the reticular formation by the stereotaxic technique described by Wilkinson.[4] In most cats the tip of the needle was found to lie about 20 mm. from the internal surface of the skull.

The needle was fixed firmly to the skull with dental cement.† Three tiny screws were buried in the bone in the frontal, occipital and central areas to serve as surface electrodes for electroencephalographic recordings. These electrodes also were covered with dental cement. The skin was closed over the entire plate of cement and around the needle. A thin layer of Silastic cement placed in the groove between the skin and the needle hub appeared to prevent infection. The three surface electrodes were attached to an amphenol plug outside the skin.

Experiments were begun the following day, after the cats were awake, alert and had demonstrated normal stance and EEG activity. All cats were eating well by the first postoperative day.

† Grip Cement, L. D. Caulk Company, Milford, Delaware.

Injection of Anesthetic Gas

A 2 ml. calibrated syringe was attached to a syringe microburet.‡ The syringe tip was inserted into a 20-inch length of plastic intravenous tubing with a nylon connector at its end. The syringe and tubing were filled with anesthetic gas from a tank. With a separate syringe, about 0.2 ml. of air was injected into the needle to make sure it was patent. A drop of water placed over the exhaust vent formed a bubble if gas was passing through the entire needle shaft. The needle was then filled with 0.10 ml. anesthetic gas which displaced the residual air in the needle. The plastic tubing either was left in position for continuous administration of gas, or it was removed and a cap placed over the needle hub (fig. 2).

When the needle tip was positioned correctly in the reticular formation, sleep was induced within a few minutes after injection of anesthetic gas. Following the injection of the gas, electroencephalographic tracings were made continuously and movies were taken. At various intervals the cats were tested for arousability and for superficial and deep pain reception. In twelve cats the same experiment was repeated one or more times each day, for up to seven days.

Injection of Volatile Anesthetic Liquids

The patency of the intracerebral needle again was tested with an injection of 0.2 ml. air, which passed into the needle shaft and out the exhaust vent. Then, 0.1 to 0.2 ml. of the liquid anesthetic was injected with a 1-ml. tuberculin syringe. The syringe was removed and the fluid in the needle gradually disappeared as the anesthetic diffused through the silicone rubber membrane into the brain. Sterile precautions were unnecessary, because both liquids and gases were sterilized during diffusion through the Silastic membrane.

Results

Gases

Teflurane ° (1,1,1,2-tetrafluro-2-bromoethane). This gas was used because its potency

‡ Syringe microburet, Model #SB22, Micro-Metric Instrument Company, Cleveland, Ohio.

° Obtained through the courtesy of Dr. Norman Wheeler, Abbott Laboratories, North Chicago, Illinois.

resembles that of cyclopropane, but it is not explosive. Therefore, EEG electrodes and EEG recorders could be used with impunity. When the needle was filled with 0.10 ml. of the gas, behavioral changes were observed within 90 seconds. Cats which were previously alert and frisky became calm and began to yawn and blink. By 3–4 minutes they crouched in a semi-prone position, and at 5 minutes put their heads down and began to sleep. At this stage they would still respond to moderate pain (i.e., pinprick on the back or hemostat closed incompletely on tail or ear) and awaken fully. When placed in a standing position, however, they would always return to the prone position and doze off. By 8–10 minutes they were asleep on their sides. At this stage some cats did not respond to light pain, while others responded sluggishly. The response for any individual cat remained about the same when the gas was injected again on a different day. The implication is that position of the needle tip may affect this pattern. The usual picture was one of sleep and hypalgesia but not total analgesia. The only hint of an excitement stage occurred in the first 2–4 minutes with a transient rise in respiratory rate in all cats. Pupils were always equal in size and there were no seizures. All cats began to awaken within 30 minutes to an hour after a single injection. They remained groggy for another 30 minutes and then resumed normal activity. They again were frisky, ate well and maintained normal stance. In four cats the entire cycle was repeated three times each day for a week and in four cats once daily during this period.

The EEG reflected the behavioral phenomena observed (fig. 3). Within two minutes of introduction of the anesthetic agent into the chemode, the cortical and depth recordings showed an increase in amplitude and a decrease in frequency. Periodic spindle bursts characteristic of light sleep appeared. During this period the animal could be aroused by sound, showing an orienting response and transient EEG desynchronization. He returned promptly to behavioral and EEG sleep. Later in the record this arousal did not occur, although the EEG record did not suggest a deeper stage of sleep. The moderately-high-amplitude, 4–6/second record with occasional

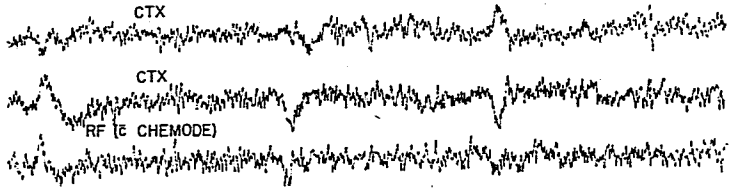
FIG. 2. Cat with intracerebral Silastic-occluded needle in the reticular formation. Plastic gas delivery tube and syringe microburet are attached. Each unit on the microburet dial represents 0.001 ml.

spindle bursts persisted until 45 minutes after induction, when a gradual transition to lighter sleep, and finally to spontaneous awakening, occurred. The post-anesthesia record was like that of pre-anesthesia. There were no lingering changes seen at the "reticular formation" electrode 1 mm. from the chemode tip. Indeed, it was striking that the mesencephalic and the cortical recordings were similar throughout.

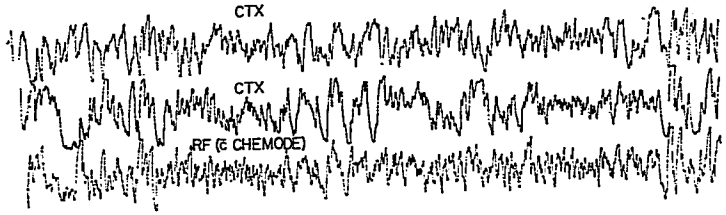
When the needle tip was positioned outside the reticular formation, no effect was observed. This occurred inadvertently in one cat. In another cat, the needle tip purposely was positioned near the third nerve nucleus, a close neighbor of the reticular formation. The cat did not become sleepy and there was no effect on the eyes.

Cyclopropane. Cyclopropane was used in three cats. The needle was filled with approximately 0.10 ml. of the gas after which a sequence similar to that produced with Teflurane was seen. However, there was a longer period (5–8 minutes) before the cats began to yawn and become sleepy. This difference cannot be ascribed to differences in potency alone because we do not know the relative permeabilities of silicone rubber to Teflurane and cyclopropane.

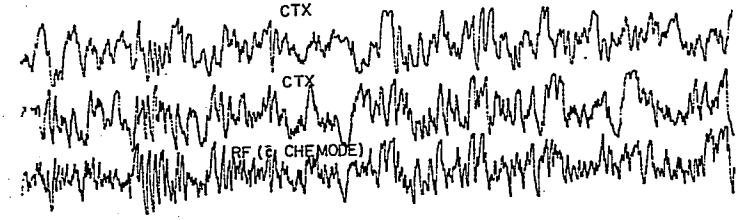
Nitrous Oxide. Nitrous oxide produced almost no effect, though it is known to diffuse very rapidly through silicone rubber.[5] With continuous passage of gas through the intra-



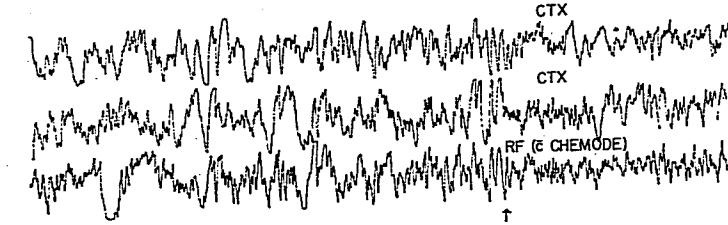
A PRE-INJECTION - AWAKE, QUIET



B DROWSY BUT STANDING



C SLEEPING



D AWAKE
(EYES OPEN)

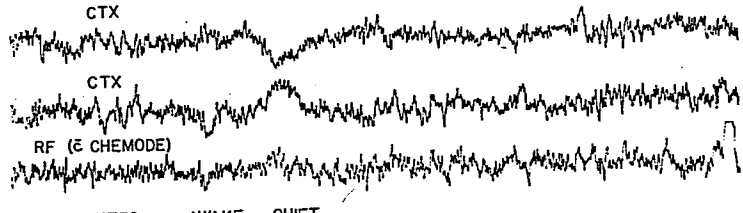


FIG. 3. (Left and above) Electroencephalogram after intracerebral Teflurane. a) Before injection, awake, standing quietly. b) One and a half minutes after injection, drowsy but standing. c) Ten minutes, asleep. d) Forty-five minutes. Beginning to awaken. e) One hundred and thirty minutes. Awake and standing.

cerebral needle, the most we could elicit was an occasional yawn or a sleep spindle on the EEG. The cats exposed to nitrous oxide included two previously injected with Teflurane, two previously injected with cyclopropane, and one nontreated cat. All remained upright and alert.

VOLATILE ANESTHETICS

Ether and Halothane. When 0.10 ml. of either of these liquid agents was introduced into the intracerebral needle, both of two cats tested had severe seizures. When the membrane was thickened by inserting Silastic cement up into the needle stem, no analgesia or anesthesia was produced. We concluded that the seizures were due to a too-rapid transfer of the volatile agents through the silicone membrane, and that this might be prevented by a membrane of appropriate thickness. Previously, we showed that ether or halothane applied directly to a Silastic shunt carrying blood will cause hemolysis unless the tubing wall is of the appropriate thickness.[2] Since it takes only a few mils to make the difference between absence of hemolysis and absence of anesthetic effect with these agents, we deferred further testing of these in the intracerebral needle until we could obtain a series of needles with membranes of increasing thickness differing by only 1–2 mils each. This study will be reported separately.

Methoxyflurane. This agent is so potent that in previous studies with shunts it produced anesthesia without any hemolysis, no matter what the wall thickness of the tubing. When 0.10 ml. was placed in the intracerebral needle in three cats, a state of sleep and hypalgesia similar to the pattern for Teflurane appeared, except that signs of sleep appeared about 12 minutes later with methoxyflurane.

Rate of Delivery of Methoxyflurane. Although we had no simple method for determining the rate of transfer of the anesthetic gases through the needle-tip membrane, we devised a rough way to measure this for methoxyflurane.

A Silastic-occluded hypodermic needle was filled with 0.1 ml. of methoxyflurane. The needle tip was placed in 1 ml. of anticoagulated blood in a small test tube which contained a magnetic spinner and which was held at 37° C. The needle was removed after 10 minutes and the blood was frozen in dry ice immediately. The needle was then dipped into another milliliter of blood for 20 minutes and this sample was frozen. When this procedure had been repeated several times, the frozen samples were mailed to Abbott Laboratories for analysis of methoxyflurane content by gas chromatography.† From their data we were able to make a rough estimate that the rate of diffusion of methoxyflurane from the needle tip was 10–20 μg./minute. This figure was variable with different needles because we have not yet standardized the thickness of the Silastic membrane at the tip. In addition, the Silastic swelled slightly as it imbibed the methoxyflurane so that the flat mem-

† Courtesy Mr. Don Robinson, Abbott Laboratories, North Chicago, Illinois.

brane surface changed to a convex one. This swelling did not occur with the gases.

Estimate of Area of Brain Tissue Exposed to Anesthetic. Sudan IV, a lipid-soluble dye, is one of the few dyes known to diffuse through Silastic.[6] Methoxyflurane was saturated with this dye and then 0.1 ml. of the reddish liquid was injected into an intracerebral needle in each of three cats, following which the typical sleep pattern occurred. After an hour each cat was sacrificed and the brain immediately perfused with formalin. The next day sections through the brain were made until the needle track was seen. At its tip was a red dot from the Sudan dye which had diffused with the anesthetic into the brain. This stained an area which extended about 1 mm. from the needle tip in all directions (fig. 4).

Discussion

The technique of injecting minute quantities of pharmacologically active agents directly into the brain is not novel. MacLean and Delgado [7] have described the injection of acetylcholine into the limbic systems of cats and monkeys. Heath and his co-workers [8] described the injection of acetylcholine into the septal regions of both schizophrenic and epileptic patients. More recently, Curtis, of the Institute of Advanced Studies, Australian National University, has devised a cluster of ultra-miniaturized pipettes that can deliver minute quantities of substances in a definite sequence to the region around a nerve cell.‡ However, we have been unable to discover any description or previous report of a method which avoids direct injection of substances into brain tissue but instead accomplishes this administration by diffusion through a membrane of selective permeability, such as we have described here.

The great permeability of silicone rubber to anesthetic gases allowed us to elicit a reproducible sleep pattern in cats. The effect was completely reversible. There was no residual functional brain damage. The anesthetic effect was specific for one area of the brain, the reticular formation. Induction time with this technique depended upon the gas used and may be related in part to the diffusion rate through silicone rubber for each gas.

The intracerebral Silastic-occluded needle had some advantages for administering substances into the brain. The anesthetic agents were sterilized during diffusion through the Silastic membrane. The rate of diffusion was uniform and stable and was a function of the area and thickness of the membrane. Therefore, maximum diffusion rate could be limited regardless of the amount of agent stored in the needle shaft. Storage of the agent and slow liberation were possible without elaborate apparatus. Gases could be administered by diffusion without mechanical disruption of brain tissue due to gas, which might occur with a direct injection.

Silicone rubber is very inert in the body. It has long been used for clinical implantation of prosthetics. It is considered by most investigators to be the most nonreactive material available for implantation into the body.

It is interesting that some of the physical properties of silicone rubber resemble those of lipid. The diffusion of anesthetics through silicone rubber may be analogous to the transport of these agents through the lipid membrane which surrounds brain cells.

Since, in addition to the anesthetics, other drugs and hormones are now known to diffuse through silicone rubber,[9, 10, 11, 12] their intracerebral administration by diffusion might profitably be explored in some clinical situations, *e.g.*, suppression of pain, suppression of seizures, or perhaps suppression of abnormal movements, by using appropriate chemical agents.

Certain basic investigations are possible, also. These might include the study of mechanisms of action of anesthetics, the study of the "second gas" effect, and the study of the effect of other silicone-diffusible drugs such as the sympathomimetic amines, in different areas of the brain and over prolonged periods. All of these agents can be investigated in a more precise fashion without the usual interfering artifacts of mechanical or pressure effects from direct injection.

Conclusion

The high permeability of silicone rubber to anesthetic gases and vapors is here applied to

‡ Personal communication, Dr. William H. Sweet.

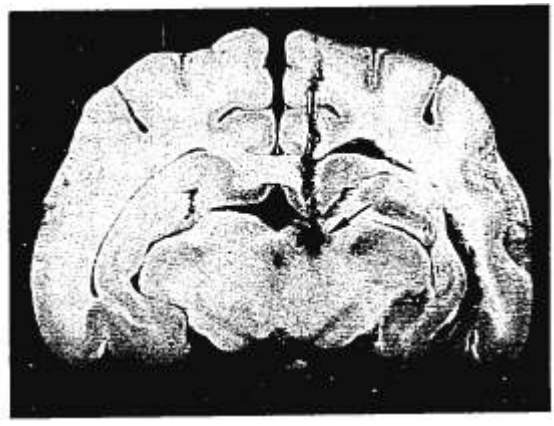


FIG. 4. Section of brain showing area of diffusion of methoxyflurane. The liquid methoxyflurane was saturated with Sudan IV and the circular area at the needle tip shows the deep staining of brain by this dye. (It is *not* a hole, although in the photograph it might be mistaken for one.) The needle tract was inadvertently dyed as the needle was removed from the brain.

the injection of these agents into the brain of the cat. A hypodermic needle with a silicone rubber membrane at its tip is inserted into the reticular formation. As little as 0.10 ml. of Teflurane, cyclopropane or methoxyflurane will produce light anesthesia when the agent is injected into the needle and allowed to diffuse through the Silastic tip into the brain.

The potential uses of this method in research anesthesia and as an approach to the treatment of intractable pain, tremor, and seizures are discussed.

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