Laboratory Note

The Toxicity of General Anesthetics Diffused Directly into the Brain

Harold A. Wilkinson, M.D., Ph.D., Vernon H. Mark, M.D., Rene Wilson, B.S., Pratap Patel, M.D.

Silastic rubber membranes are permeable to most general anesthetics, but are impermeable to bacteria.1 2 3 When fashioned into “chemodes,” these membranes can be permanently implanted within the brain, permitting repeated aseptic introduction of various agents directly into selected focal brain areas. Since the agents enter the brain by diffusion, no mechanical tissue distortion results.

Our previous studies4 demonstrated that sleep could be induced safely in cats by diffusing the anesthetic gas Teflarane (Abbott-16900, kindly supplied by Abbott Laboratories, North Chicago) into various areas of the reticular activating system. The chemodes themselves elicited little or no tissue reaction, and the Teflarane was well tolerated.

Unfortunately, Teflarane is not available for general use, despite its safety and effectiveness in this limited application. In search of an alternative agent, we have surveyed four volatile general anesthetic liquids—both in liquid and in vapor form.

Methods

Thirty-six chemodes were successfully tested in the brains of adult cats. The devices employed were of the same design as those described in our previous publication.4 Each chemode was stereotaxically implanted aseptically with the cat under barbiturate anesthesia, and was anchored in place for chronic use. All chemodes in this series were implanted within either the thalamic reticular activating system or frontal white matter. Electrodes for EEG recordings were included with each chemode; additional ball electrodes were placed subdurally for parietal and frontal cortical recording.

After a one-week recovery period, each cat was tested on four different days over a two-week period. The same agent in the same form (liquid or vapor) was introduced into each chemode over a period of one hour on each of the four test days. Behavioral results were recorded in terms of induced sleep, with a concomitant analysis of EEG tracings for slow waves and sleep spindles. At the conclusion of the test period, the animals were anesthetized and their brains were perfused in situ with formalin–saline solution. Each chemode was tested for leaks by postmortem instillation of methylene blue dye, which does not cross an intact silastic membrane. The hardened brain was then sectioned, stained with hematoxylin and eosin, and examined microscopically.

The four general anesthetics employed in this study were diethyl ether, halothane (Fluothane), methoxyflurane (Penthrane), and trichlorethylene (Trilene). Each was administered either as a liquid or as a saturated vapor in oxygen. When a liquid form was used, the active chemode chamber and chemode reservoir were simply filled with the undiluted agent, the rate of diffusion being determined by “pore size” and wall thickness of the membrane. Vapor-saturated oxygen was introduced at a slow rate into the active chamber and allowed to escape through the vent tube into the atmosphere for vapor-phase testing.
TABLE 1. Severity of Tissue Damage Caused by General Anesthetics Administered Intracerebrally through Chemoses*

<table>
<thead>
<tr>
<th></th>
<th>Toxicity in Liquid Form</th>
<th>Toxicity in Vapor Form</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimal</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Halothane</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

* Number of chemode sites showing minimal or moderate to severe focal necrosis and gliosis. “Minimal” = tissue damage of less than 1 mm surrounding the chemode; “moderate-severe” = tissue damage of more than 1 mm surrounding the chemode.

Results

Behavioral results of focal intracerebral diffusions proved more difficult to assess in this series of cats than in the earlier series receiving Teflurane intracerebrally. Many of the animals sustained neurologic damage from the agents used in this study, and were already drowsy or obtunded at the time of testing. In

Fig. 1. Whole-brain section, showing extensive necrosis at the site of a chemode perfused with liquid halothane. The central rectangular vacant area represents the site of the chemode, which was removed after fixation of the brain, but prior to microtome sectioning.
general, neurologic deficits were more frequently seen and more severe in those cats injected with anesthetic agents in liquid form. Animals which received vapor-phase anesthetics sustained less neurologic damage, but also showed little tendency to become sleepy. Cats with thalamic chemodes generally developed more severe neurologic deficits than did those with frontal chemodes; they generally tended to become drowsy, but rarely went completely to sleep. Observed behavioral changes were approximately the same for all four agents tested.

Histologic examination disclosed that each of the four agents caused significant local destruction of cerebral tissue when diffused through intracerebral chemodes in liquid form. Tissue damage also resulted when these agents were used in vapor form, but was less consistent (table 1). Histologically, the areas surrounding the chemodes showed extensive necrosis and reactive gliosis (figs. 1 and 2). Microglia were frequently present; polymorphonuclear cells were less commonly found. None of the chemodes developed leaks and no focal infections were found.
Discussion

Chronically implanted intracerebral chemodes represent a potentially useful new tool for chemical exploration of focal areas of the brain. The devices themselves have been demonstrated to be safe and nontoxic in use in experimental animals. Unfortunately, this study has shown that many agents which diffuse through silastic rubber membranes and which are relatively safe when used in routine systemic fashion may be quite toxic to cerebral tissue when allowed to diffuse focally intracerebrally. This proved to be the case with all four agents tested in this study; diethyl ether, halothane, methoxyflurane, and trichloroethylene.

Despite the discouraging results of this study, silastic membrane chemodes have proven practical and safe in use with the anesthetic gas Teflurane. Other silastic membrane devices have been used successfully in other areas of the body: heart, subcutaneous tissue, and blood stream. Many of the biogenic amines seem also to pass harmlessly through chemodes into the brain. Continued testing of other available tissue depressants and other types of membranes will undoubtedly reveal further areas of usefulness for these devices, not only in anatomic–neurochemical and neurophysiologic research but in clinical applications as well.

Summary

Chemodes with silastic rubber semipermeable membranes which have been chronically implanted in the brains of cats have been used to diffuse four general anesthetics into focal areas of the brain. These agents (diethyl ether, halothane, methoxyflurane and trichloroethylene) all proved extremely toxic to brain tissue. Although other compounds have been shown to be safe and effective when introduced into the brain through chemodes, caution is warranted in using agents whose safety in this application has not been proved.

References


Drugs and Their Actions

PROPRANOLOL IN HYPERTENSION Effectiveness of long-term propranolol therapy in reducing arterial pressure was evaluated in 48 patients with either essential or renovascular hypertension. All patients received this drug only. Approximately half responded with significant decreases in arterial blood pressure; the other half did not, but cardiac outputs were decreased in both groups. The decrease in arterial pressure appears to have been caused by a substantial decrease in peripheral vascular resistance, although the mechanism for this change is not known.