associated with pressures well in excess of 60 cm H₂O. Fasciculations caused by depolarizing muscle relaxants can raise gastric pressure to more than 20 cm H₂O, in some cases, more than 40 cm H₂O. However, total paralysis provided by adequate doses of relaxants can prevent the rise in gastric pressure caused by vomiting, and there is now evidence that small doses of nondepolarizing muscle relaxants given three to six minutes prior to depolarizing agents will prevent the increased gastric pressure observed during fasciculations.

The proper selection of patients is very important when considering the use of crush induction with cricoid pressure to prevent regurgitation. The patient must be evaluated in terms of his ability to tolerate a large dose of intravenous inducing agent, since it is of paramount importance that anesthesia be induced rapidly to prevent struggling and excitement. The anesthesiologist must also make a judgment as to the ease with which a given patient can be intubated. Should any of the commonly-recognized barriers to easy intubation exist (very prominent incisors, receding mandible, facial fractures, etc.), alternative methods of inducing general anesthesia should be considered. Since facility at intubation is so frequently related directly to the skill of the anesthesiologist, this technique appears to be too risky for neophytes except under the closest possible supervision.

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REFERENCES

The Search for Better Anesthetic Agents: Clinical Investigation of Éthane

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There are currently available at least four potent inhalation anesthetic agents whose hu-
customized to the blood-pressure stability seen during cyclopropane anesthesia. Halothane's deficiencies include lack of good analgesia, inadequate muscle relaxation, and sensitization of the myocardium to catecholamines. Perhaps the greatest concern about halothane today is that generated by the suggestion that it produces drug-induced hepatitis. While there is little solid evidence of a cause-and-effect relationship between the administration of halothane and the occurrence of hepatitis, nonetheless there certainly are coincidental relationships in enough instances to cause concern. Methoxyflurane does not sensitize the myocardium to catecholamines and provides better analgesia than halothane, but it is so soluble in blood that induction and emergence from anesthesia are prolonged and the drug remains in the body for a considerable length of time.

For these reasons, we have continued to investigate new inhalation anesthetics. This report summarizes our experiences with a new agent, Ethane, and raises philosophic considerations regarding its present status. We believe little purpose would be served by detailing the pharmacologic data we have recorded, since others have done so and our data are substantially the same as theirs.\footnote{For those interested, tabular data will be supplied with reprints requested.}

**Methods**

Ethane \footnote{\textcopyright Trademark, Air Reduction Co., Inc.} (Ohio Compound 347, 2-chloro-1, 1,2-trifluoroethyl difluoromethyl ether) is a volatile liquid with a mild ethereal odor. It boils at 56.5°C, has a vapor pressure of 184 torr at 20°C and a blood gas distribution of 1.9 at 37°C, and is nonflammable in all concentrations in air, nitrous oxide and oxygen. It is stable in the presence of light and oxygen and does not require the addition of chemical stabilizers.\footnote{Permission was elicited from each patient (or his guardian) to administer an experimental inhalation anesthetic agent to him. He was told that this was a new drug which had been thoroughly studied in animals and had been given to several hundred patients and that we were evaluating its usefulness and safety further. Each patient (or his guardian) signed a consent form.}

We have administered this agent to 304 patients and one volunteer subject.\footnote{These individuals, 191 of whom were male, ranged in age from 5 to 90 years. The majority were in ASA physical status 1 or 2, but 75 were classified in status 3 or 4. Although surgical operations on all areas of the body were included in the study, the majority (229) were neurosurgical procedures, mainly laminectomies and craniotomies, and required between one and four hours for completion. The drug was administered using Vernitol or Copper Kettle vaporizers or a Fluotec vaporizer recalibrated for Ethane. In most patients anesthesia was induced with a sleep dose of thiopental (Pentothal); Ethane was supplemented with nitrous oxide in half of the patients. Blood or urine specimens from 38 of the patients were subjected to routine pre- and postoperative laboratory tests. Blood studies (hemoglobin, hematocrit, total and differential leukocyte counts), urinalysis (specific gravity, pH, albumin, sugar, microscopic examination of sediment), and determination of SGOT for 22 of the 38 patients were done preoperatively and on the first, third and fifth postoperative days. For another 16 patients, analyses of blood for alkaline phosphatase, total bilirubin, SGOT, total protein, albumin, BUN, glucose, bicarbonate, calcium, sodium, potassium and chloride were performed preoperatively and on the second, fifth and seventh postoperative days. Respiratory volumes of 90 patients receiving Ethane in oxygen were measured with a Wright Respirometer. Electrocardiograms of 60 patients were observed with an oscilloscope monitor. The electroencephalograms of four patients, recorded before and periodically during Ethane anesthesia, were subjected to detailed frequency analysis using a digital computer. Blood samples drawn at the time of the EEG recordings were analyzed by gas chromatography for Ethane content and by blood-gas electrodes for oxygen and carbon dioxide tensions and pH.}

**Results**

Induction of anesthesia with Ethane and oxygen proceeded at about the same rate as induction with halothane and oxygen; mild excitement occurred in some patients. The tracheas were intubated without muscle re-
laxants in some cases; however, in most instances succinylcholine or another muscle relaxant was used to facilitate intubation. The inspired concentration of 

\textit{Éth}rane required for the maintenance of anesthesia ranged between 1 and 6 per cent; most patients required 2.5 to 3 per cent. Satisfactory anesthesia could be provided by 

\textit{Éth}rane alone. With the exception of the rare symptoms of central nervous system irritability described below, there were no unusual complications attributable to the use of 

\textit{Éth}rane.

Pulse and electrocardiographic irregularities were rare. In a few instances transient nodal rhythm was observed, and bradycardia following a second dose of succinylcholine was evident on the electrocardiogram of one patient. Cardiac rates were remarkably stable during 

\textit{Éth}rane anesthesia. Blood pressures tended to decrease following induction of anesthesia, an effect most pronounced in those patients whose blood pressure had been elevated prior to induction. In approximately 60 per cent of the patients, blood pressures decreased more than 10 torr. In the remaining 40 per cent, blood pressures were unchanged or slightly increased.

Respiration during 

\textit{Éth}rane-oxygen anesthesia and operation was slightly depressed. Respiratory rates tended to be elevated, with tidal volumes decreased, resulting in minute volumes which were approximately normal. Respiratory rates did not vary with depth of anesthesia, but tidal volumes decreased as anesthesia was deepened. We found it necessary to assist respiration in deeper planes of anesthesia to keep $P_{\text{aCO}}$ below 50 torr in the study of the EEG.

No remarkable changes in the blood or urine were observed. In seven patients, SCOT values were elevated at some time during the first five postoperative days, but these had returned to normal or nearly so by the seventh day.

Adequate muscular relaxation and analgesia for most surgical procedures were provided by 

\textit{Éth}rane and oxygen or nitrous oxide. It was not always possible, however, to provide adequate surgical conditions without excessive depression of the blood pressure; consequently, muscle relaxants (d-tubocurarine; succinylcholine) were used as required to avoid deep anesthesia. Anesthesia was provided for three cholecystectomies and two diaphragmatic herniorrhaphies without the use of significant amounts of muscle relaxants. In some instances, responses to surgical stimuli occurred even when the depths of anesthesia appeared adequate as judged by inspired concentration, muscular relaxation, or depression of blood pressure. Recovery from anesthesia ordinarily was rapid and uneventful. During the recovery periods two of 151 patients had nausea, one vomited, and 17 shivered. There was no apparent relation between shivering and body temperature.

Increases in electrical activity at all frequencies were observed in the EEG as the concentration of 

\textit{Éth}rane was increased, resulting in the development of appreciable high-frequency activity at high anesthetic concentrations. Somewhat similar effects have been observed with methoxyflurane, whereas high-frequency activity has not been observed with fluroxene,\textsuperscript{9} cyclopropane or halothane anesthesia.\textsuperscript{10}

Six patients showed signs of central nervous system irritability, manifested as twitching movements of the jaw or neck or, occasionally, the extremities and body. Three were men without histories of neurologic disease and three were grossly hydrocephalic children who had had multiple operative procedures to reduce skull sizes and intracranial pressures. In two of these six patients, the symptoms appeared spontaneously; in the other four, they resulted from deliberate attempts to explore the precipitating factors of the excitability.

One patient, a 36-year-old man, was anesthetized with 

\textit{Éth}rane and oxygen for bilateral ligation and stripping of varicose veins. No other anesthetic or sedative drug was used. A seizure occurred after the patient had been anesthetized for almost two hours, 12 minutes after the beginning of controlled respiration. Five minutes earlier the patient had responded to surgical stimuli, so the anesthetic concentration into the breathing system had been increased from 3 to 7 per cent and then to 9 per cent. The seizure, which was mild, was confined to the neck muscles, and disappeared with decreases in anesthetic concentration and respiratory rate. At the time of the seizure, the arterial 

\textit{Éth}rane concentration was 3.3 vol-
umnes per cent. The EEG pattern consisted of a few spikes and slow-wave complexes but was largely obscured because of movement artifact. Hypotension from 100/65 to 55/35 torr lasted for six minutes following the seizure. About an hour later another seizure occurred. The anesthetic concentration being delivered to the system had been 6.6 per cent for about 20 minutes and respirations were being controlled at 9 per minute. The seizure was again mild, restricted to neck and chest muscles, and followed by hypotension for three minutes. The arterial anesthetic concentration at this time was 4.6 volumes per cent. Approximately half an hour later another convulsion occurred, four minutes after the anesthetic concentration delivered to the circle system had been increased from 4.5 to 9 per cent. Hypotension was not observed. Arterial anesthetic concentration was 3.5 volumes per cent. The EEG pattern consisted of 30 seconds of spikes at a frequency of 1 to 8 Hz, preceded by a minute of spike-wave complexes at irregular intervals of 1 to 6 seconds. The spike pattern was followed by 45 seconds of electrical silence and then by five minutes of spike-wave complexes every 2 to 8 seconds. An EEG several days later was interpreted within normal limits.

Two other men, 34 and 57 years old, had seizures during anesthesia. In neither case was past medical history contributory, and both patients recovered without sequelae. The seizures occurred during controlled respiration and moderate-to-deep Ethrane anesthesia. Hypotension was not seen following the seizures in these patients.

Convulsive movements during Ethrane anesthesia also appeared in three grossly hydrocephalic children. All had had repeated operative procedures and one had a history of spontaneous seizures. Preanesthetic medication was omitted and anesthesia was induced with Ethrane or nitrous oxide. One, a 9-year-old girl, was anesthetized three times with Ethrane and manifested twitching each time. Inspired anesthetic concentrations ranged from 2.4 to 7 per cent. Twitching stopped when the inspired Ethrane concentrations were decreased. A 7-year-old boy was anesthetized twice with Ethrane, and an 11-year-old boy, four times. Twitching occurred both times with the 7-year-old and two of the four times with the 11-year-old. The twitching could be produced or stopped by increasing or decreasing the anesthetic concentration.

**DISCUSSION**

Pharmacologically and chemically, Ethrane behaves like halothane, although its chemical structure more closely resembles that of methoxyfluorane. This similarity is probably due to the two highly-electronegative fluorine atoms on the carbon atoms on either side of the oxygen atom, which reduce the influence of the ether-oxygen and make Ethrane behave more like a hydrocarbon. The pharmacologic advantages of Ethrane over halothane are relative freedom from cardiac arrhythmias, better muscular relaxation and analgesia, and greater chemical stability. The only important drawback that we have observed is the appearance of central nervous system excitability in approximately 2 per cent of our patients and, as mentioned, in four of the patients this complication occurred as we were exploring the predisposing causes of the excitability. In no case was the motor activity observed as extensive or severe as the fasciculations which often follow intravenous injection of succinylcholine. The movements were not greater than the running movements seen during divinyl ether anesthesia. In all instances the excitability could be terminated by lightening anesthesia, reducing the minute ventilation, or changing anesthetic agents. Postoperative sequelae were not observed.

These studies have raised certain questions in our minds. Should we continue to study a drug which provides good anesthesia with excellent cardiac stability but also stimulates the central nervous system in a few patients? Certainly, we could block the motor activity with a muscle relaxant. In most cases we avoided using concomitantly agents that would obscure the effects of Ethrane. Dobkin and his co-workers did not observe this complication when using the agent in combination with thiopental, muscle relaxants and narcotics, a technique more akin to common anesthetic practice.

Is this drug worth a greater clinical trial? It already has been used in about 3,000 patients, and no evidence of harm from its use...
has appeared. An important question is whether the Food and Drug Administration might approve this drug for further clinical trial or for general distribution. With the current, unresolved dilemma concerning halothane and the liver, it is conceivable that we may suddenly need another well-studied, non-flammable inhalation anesthetic agent. Methoxyflurane, with its low volatility and high solubility, is not a good alternative. Should we, therefore, continue to study Ethrane on a broader scale, in the hope that it will fulfill the role of an alternative drug to halothane? Would anesthesiologists be more comfortable with a drug that produces visible, harmless muscular activity than with the threat of poorly-understood hepatic dysfunction post-operatively?

We believe more data about this agent should be accumulated through its use by more anesthesiologists in a larger number of patients.

**SUMMARY**

The search for an ideal anesthetic agent has led to the synthesis and study of many chemicals. Each agent introduced into clinical practice has had drawbacks, and the search continues. One volatile liquid currently being investigated shows considerable promise, although it, too, has a drawback which may keep it from ultimate acceptance. This drug, Ethrane (Ohio Compound 347), provides satisfactory inhalation anesthesia alone or in combination with nitrous oxide when administered at a maintenance concentration of approximately 3 percent. Cardiac rhythm and pulse are stable, while blood pressure decreases following induction of anesthesia. Respiration is depressed with increasing depth of anesthesia. Muscular relaxation and analgesia are better than those observed with halothane. Emergence from anesthesia is rapid, with a low incidence of nausea and vomiting. However, symptoms of central nervous system excitability, without sequela, have appeared in 2 percent of our patients. We believe that the appearance of this response should not deprive Ethrane of further study.

**REFERENCES**


