ANESTHESIA LX: THE ANESTHETIC PROPERTIES OF 1,1,1-TRICHLOROETHANE

JOHN C. KRANTZ, JR., PH.D., CHUNG S. PARK, M.D., JOHNSON S. L. LING, PH.D.

THERE has been a revival of interest in the use of halogenated hydrocarbons and ethers as anesthetic agents.[1, 2] Some years ago one of us (J. C. K., Jr.) with Forman [3] studied 1,1,1-trichloroethane (TCE) in laboratory animals as an anesthetic agent but abandoned the experiments owing to the toxicity of the compound. More recently TCE has been prepared in a pure form and is available at low cost. Therefore we were prompted to restudy its anesthetic properties. Lazarew,[4] using mice, found the ratio between the concentration of vapor causing the loss of reflexes and death from chloroform to be 15, and that of TCE, 20.

TCE is a clear, colorless mobile liquid which boils at 74.1 C., and is nonflammable. The odor of its vapors resembles chloroform. The density of TCE is about 1.44 at 20 C. The liquid is preserved against deterioration by the addition of 0.01 per cent of thymol.

EXPERIMENTAL

Observation Anesthesias. Four dogs and 2 *Macacus rhesus* monkeys were anesthetized with TCE. The technique employed has been described previously.[5] The period of induction was short and resembled that with chloroform. During induction there was breath-holding in some animals. Salivation was minimal, and the bronchial tree remained free from mucus during the anesthesia period of 30 minutes. Surgical anesthesia was uneventful; breathing was deep and regular and often stertorous. Relaxation of the abdominal musculature and extremities was good. Occasionally an animal exhibited incoordinated leg movements during anesthesia. Pain reflexes were absent during surgical anesthesia, and analgesia appeared to extend into the recovery period. Recovery from anesthesias of 20 to 30 minutes' duration occurred in 2 to 5 minutes, and was, as a rule, tranquil. The quantities of TCE required were approximately equal to those of chloroform needed to produce comparable anesthesia.

Anesthetic Index. The anesthetic index of TCE was determined on monkeys and dogs as previously described.[6, 7] The data shown in tables 1 and 2 indicate that TCE is a potent anesthetic agent. In the dog and monkey there is no statistically significant difference between the anesthetic index of TCE and Fluothane.[7] The potency lies between those of Fluoromar and Fluothane. The difference between the means of the volumes required to produce respiratory arrest and surgical anesthesia in the dog is 0.26 ml./kg. Our corresponding value for chloroform was 0.27–0.17 or 0.1 ml./kg.[8] This is indicative of a greater margin of safety for TCE than for chloroform.

Electrocardiographic Studies (Monkeys and Dogs). Six dogs and 2 monkeys were anes-

TABLE 1

ANESTHETIC INDEX* OF TRICHLOROETHANE IN DOGS

Dog	Weight (kg.)	Induction (ml./kg.)	Respiratory Failure (ml./kg.)	Anesthetic Index
1	7.0	0.36	0.68	1.90
2	11.0	0.36	0.57	1.56
3	17.0	0.29	0.62	2.10
4	17.9	0.17	0.29	1.75
5	8.2	0.37	0.55	1.50
6	9.3	0.43	0.62	1.44
7	9.3	0.38	0.73	1.93
8	11.5	0.22	0.35	1.60
9	7.8	0.45	0.93	2.07
10	7.8	0.38	0.90	2.33
11	8.3	0.30	0.39	1.30
Mean		0.34	0.60	1.77
σ		0.90	0.21	0.33
C.V.		26.47	35.00	18.64

* The anesthetic index is obtained by dividing the volume of agent in ml./kg. required for respiratory failure by the volume in ml./kg. required for induction of the animal into surgical anesthesia.

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TABLE 2

ANESTHETIC INDEX* OF TRICHLOROETHANE IN MONKEYS (*Macacus rhesus*)

Monkey	Weight (kg.)	Induction (ml./kg.)	Respiratory Failure (ml./kg.)	Anesthetic Index
1	3.5	0.21	0.43	2.00
2	2.1	0.23	0.60	2.49
3	2.7	0.28	0.56	2.00
4	2.0	0.38	1.00	2.66
5	2.1	0.24	0.60	2.50
6	2.7	0.28	0.46	1.66
7	3.5	0.29	0.50	1.75
8	3.5	0.21	0.43	2.00
9	2.7	0.28	0.65	2.33
10	2.1	0.36	0.71	2.00
Mean		0.28	0.59	2.15
σ		0.06	0.17	0.33
C.V.		21.42	28.81	15.34

* The anesthetic index is obtained by dividing the volume of agent in ml./kg. required for respiratory failure by the volume in ml./kg. required for induction of the animal into surgical anesthesia.

thetized with TCE by a closed technique. Deep surgical anesthesia was maintained for 60 minutes. Electrocardiograms were recorded and compared with those observed prior to anesthesia (fig. 1). The pattern of the electrocardiogram was essentially unaltered. The heart rate was increased under anesthesia and the T-wave was either flattened or inverted. The electrocardiographic pattern at the point of respiratory arrest showed depressed ST-segments; tachycardia was absent and mild bradycardia prevailed.

Blood Pressure Studies (Dogs). Blood pressure studies were conducted on dogs anesthetized with TCE and ethyl ether by a closed circuit technique. The blood pressure was recorded by a mercury manometer from the carotid artery. The respiration was measured by a tambour connected to the trachea. From figure 2 it is clear that anesthesia with TCE elicited a depressor response. At the point of respiratory arrest the blood pressure was reduced to approximately one-half of its normal value. This is in contrast to ethyl ether anesthesia, as shown in the figure, where at threatened respiratory arrest the blood pressure is only slightly depressed.

Effect on the Perfused Heart of the Frog. TCE was dissolved in Howell-Ringer's solution and perfused through the frog's heart *in situ*. Solutions containing 10, 20 and 40 mg. per cent were employed on 6 frogs. It is apparent from figure 3 that concentrations up to 20 mg. per cent produce little diminution in the amplitude of heart beat. Forty milligrams per cent concentration decreased the amplitude of heart beat to approximately one-third of normal.

Effect on Oxygen Uptake of Rat Heart. Rats were deeply anesthetized with TCE or chloroform for an interval of one hour, whereupon the heart of each animal was immediately removed. Cardiac ventricular slices were promptly prepared and the oxygen uptake over a one-hour interval was measured, using the Warburg technique with a glucose substrate.[9] These data were compared with those from unanesthetized control rats. In 4 control experiments the mean Q_{O_2} was 9.76 ± 0.43. In 6 experiments with TCE-anesthetized rats the mean Q_{O_2} was 6.51 ± 1.06. In 6 additional experiments using chloroform the mean Q_{O_2} was 6.88 ± 0.83. TCE anesthesia evoked a 33.3 per cent diminution in the oxygen uptake of the myocardium which was considered

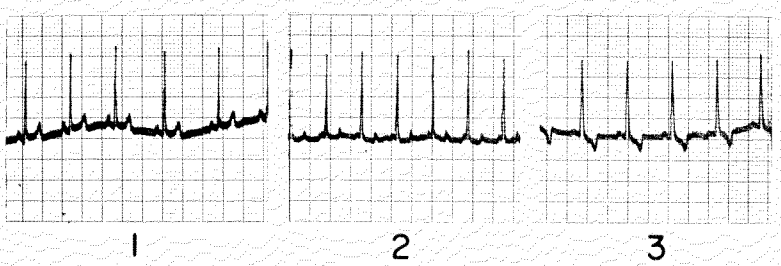

FIG. 1. Electrocardiogram of dog under trichloroethane (TCE) anesthesia. Lead II. (1) Normal dog; (2) TCE surgical anesthesia; (3) TCE respiratory arrest.

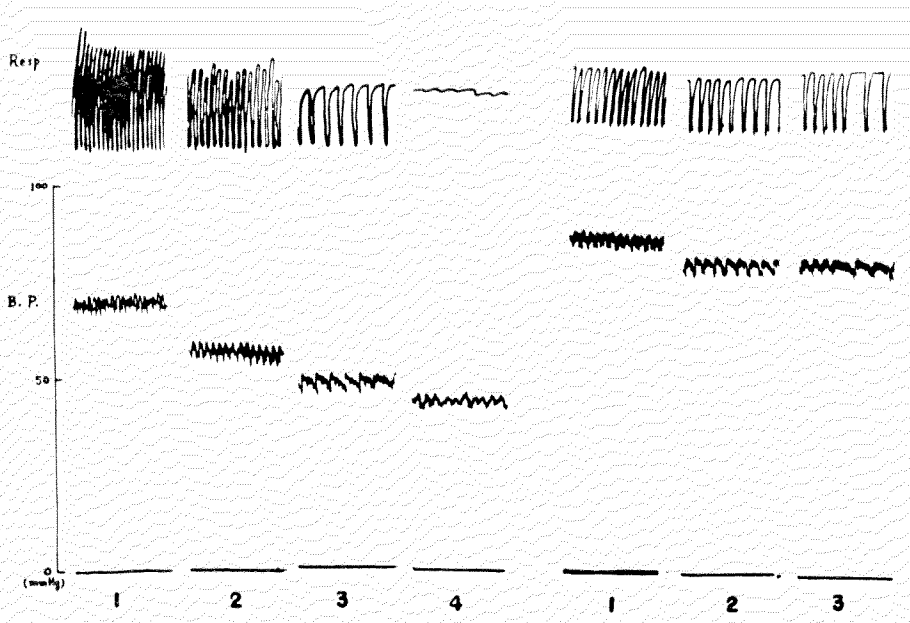

FIG. 2. Blood pressure and respiration of the dog under trichloroethane (TCE) and ethyl ether anesthesia. Left—TCE. (1) Light surgical anesthesia; (2) deep surgical anesthesia; (3) threatened respiratory arrest, and (4) respiratory arrest. Right—diethyl ether. (1) Light surgical anesthesia; (2) deep surgical anesthesia, and (3) threatened respiratory arrest.

significant. Chloroform also depressed the oxygen utilization of the heart muscle as indicated by a 29.5 per cent decrement.

Liver Function Tests in the Dog. Three dogs were subjected to the Bromsulfalein liver function test. Prior to and one hour after 60 minutes of anesthesia with TCE the test was repeated. After 24 and 72 hours the test was performed again. The percentage of dye excreted in no case was significantly greater than the preanesthetic values.

Plaa *et al.*[10] developed a new method of detecting hepatic damage produced by halogenated hydrocarbons. Using mice, these investigators measured the increase in sleeping time evoked by a subcutaneous injection of the halogenated compound in oil when pentobarbital was administered. Of seven compounds

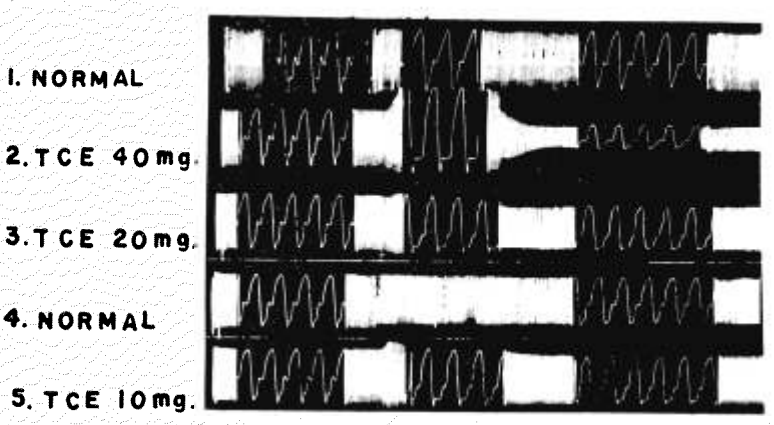

FIG. 3. Perfused frog heart with trichloroethane (TCE). Mg. = milligrams per cent.

TABLE 3

OXYGEN CONSUMPTION OF MONKEY UNDER TRICHLOROETHANE (TCE) ANESTHESIA

	Normal		TCE		Difference	
	Respirations/ Minute	O_2 Uptake (ml./kg./hour)	Respirations/ Minute	O_2 Uptake (ml./kg./hour)	Respirations/ Minute	O_2 Uptake (per cent)
2.1 kg. 1	56	3,238	55	2,095	− 0	−1,142 (35.3)
M 2	58	3,428	61	2,857	+ 3	−571 (16.7)
3	54	2,380	69	1,714	+15	−666 (28.0)
2.7 kg. 1	52	2,370	58	1,925	+ 5	−444 (18.8)
M 2	79	3,555	77	2,074	− 2	−1,481 (41.7)
3	34	1,857	58	1,037	+24	−814 (44.0)
3.5 kg. 1	52	1,942	61	1,571	+ 9	−471 (19.1)
F 2	68	2,628	66	2,342	− 2	−285 (10.9)
3	76	3,428	75	1,771	− 1	−1,757 (51.3)
				Mean		26.7
				S.D.		±14.5

tested by this method, including chloroform and trichloroethylene, TCE was found to be the least hepatotoxic.

Repeated Anesthesia in the Rat. Four rats were anesthetized with TCE for 1 hour on three consecutive days, 4 rats on six consecutive days and 4 rats on nine consecutive days. One animal died after 6 anesthesias and another after 8 anesthesias. All animals were ultimately sacrificed and histologic studies were made of the brain, spinal cord, liver and kidneys. No significant pathologic changes were present with the exception of those found in the liver of one rat exposed to 9 anesthesias. In this specimen there was evidence of midzonal necrosis of the hepatic parenchyma.

Clotting Time and Hemolysis of Blood in the Dog. The clotting time of blood was determined in 4 normal dogs by the capillary tube method. The average clotting time was about 60 seconds. Under deep surgical anesthesia with TCE of 60 minutes' duration, the clotting time was again determined. No significant change was noted.

Volumes of 10 ml. of TCE of varying concentrations in normal salt solution, to which was added 0.1 ml. of defibrinated dog's blood, were maintained at 25 C. for 24 hours. No hemolysis was observed by concentrations of 50, 100 and 150 mg. per cent of TCE.

Preanesthetic Medication. In 2 dogs, inducing TCE anesthesia with nitrous oxide-oxygen or cyclopropane-oxygen mixture was uneventful. Preanesthetic medication with pentobarbital sodium or morphine was found to be compatible with TCE anesthesia in 2 dogs.

Respiratory Effect Under Deep Anesthesia. The data in table 3 show the effect of deep TCE anesthesia on the respiratory rate and oxygen consumption of the monkey, using a Benedict-Roth respirometer. The animal was anesthetized by the anesthetic index technique until the quantity of TCE administered was 50 per cent of that previously required for respiratory arrest. The oxygen consumption was measured again for a period of 6 minutes, during which anesthesia was maintained by the administration of 0.05 cc. of TCE per minute.

The depression of oxygen uptake under TCE anesthesia is approximately twice as great as that under Fluoromar [1] anesthesia and is comparable to the depressions of oxygen uptake under chloroform and Fluothane anesthesias, respectively.[2]

Irritation of the Mucous Membranes. As a first approximation of the irritative properties of TCE, the agent dissolved in corn oil was instilled into the conjunctival sac of six rabbits. Solutions of 5 per cent by volume were prepared and compared with a similar solution of chloroform. One drop of the oil solution was used in one eye and one drop of the chloroform solution in the contra-lateral eye. The conjunctivas were observed periodically over a 12-hour period. The chemosis and hyperemia elicited by TCE appeared to be comparable to that provoked by chloroform.

Flammability of Vapor. The vapor of TCE is not flammable.

Solubility in Water. van Arkel [11] determined the solubility of TCE in water to be 0.27 gm. (0.19 ml.) in 100 ml. at 30 C. Referring to the curve of Carr *et al.*,[12] in which water solubility is plotted against oil/water coefficient, the oil/water coefficient of TCE was found to be approximately 100. This physical constant bespeaks a high anesthetic potency which was observed in all our animal studies.

Having completed these experiments, on December 1, 1957, Dr. Paul R. Hackett administered TCE by a closed circuit method to a volunteer, aged 30. Induction was smooth and anesthesia was maintained uneventfully for 30 minutes. There were no significant electrocardiographic changes during anesthesia. The blood pressure dropped to 70 per cent of preanesthetic level. Recovery was slow, but uneventful. The individual complained of being tired for several hours after the anesthesia.

Summary

Trichloroethane is a volatile liquid with potent anesthetic properties comparable to those of chloroform. No functional hepatic impairment was shown in the dog by the Bromsulfalein test, nor did repeated anesthesias in the rat with TCE produce kidney or liver damage except in one animal after nine anesthesias. The electrocardiogram of the monkey and dog failed to change significantly, but the blood pressure of the dog was markedly depressed by TCE. Oxygen uptake was depressed in the monkey by anesthesia with TCE.

This first approximation of the anesthetic properties of TCE warrants its cautious trial in man.

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PREANESTHETIC ROOM A distinctive feature of a large, cheerfully painted preanesthetic room is a painting of a detailed scene on the ceiling illuminated indirectly from valences. Of 100 patients questioned 80 per cent noted and most liked it. A variety of reasons why and how it helped alleviate anxiety is advanced. Very few patients had no memory of seeing it. (*Steel, G. C.: Decoration of the Anesthetic Room: A Study of Patients' Reactions, Brit. M. J. 1: 43 (Jan. 3) 1959.*)

DIRTY SHOES Cultures were made from 15 surgeons' and 15 obstetricians' shoes taken from lockers in surgery and obstetrics. Cultures from every pair of shoes had multiple colonies including 23 strains of hemolytic staphylococci, 5 strains of Proteus, 50 beta-hemolytic gram-positive rods, and numerous fungi. The antibiotic resistance of these organisms indicated that they were lately associated with clinical infections treated with antibiotics during which resistance developed. These were shoes which were kept in the delivery or surgical suite so that hospital dirt would not be tracked into the operating or delivery suites. The plea is made that shoes should be placed in a washing machine at the end of an operation or delivery or sterilized with ultra-violet sterilization. The alternative would be the use of easily laundered cloth covers in pediatric, obstetric and surgical areas. (*Casey, A. E., and others: Shoes as a Potential Hazard to Surgical and Obstetrical Patients, South. M. J. 52: 384 (April) 1959.*)