CARDIOPULMONARY TOXICITY OF TETRACHLOROETHYLENE

Shinichi Kobayashi, Duncan E. Hutcheon, John Regan

Departments of Medicine and Pharmacology,
College of Medicine and Dentistry of New Jersey,
Newark, New Jersey

Tetrachloroethylene (1,1,2,2-tetrachloroethene) is a widely used organic solvent capable of producing adverse renal, hepatic, and central nervous system effects. The cardiac effects of tetrachloroethylene, thus far unexplored, were studied in several species. To standardize the dosimetry, tetrachloroethylene was prepared for intravenous injection in solutions of Tween 80, which had no demonstrable cardiotoxicity. In rabbits under urethane and in cats and dogs under pentobarbital, tetrachloroethylene increased the vulnerability of the ventricles to epinephrine-induced extrasystoles, bigeminal rhythms, and tachycardia. The mean threshold doses of tetrachloroethylene were 10 mg/kg in rabbits, 24 mg/kg in cats, and 13 mg/kg in dogs. In rabbits this threshold dose for cardiac arrhythmias corresponded to blood levels between 2.2 and 3.6 μg/ml. Animals demonstrating a reflex bradycardia to vasopressor doses of epinephrine were relatively resistant to the arrhythmogenic action of tetrachloroethylene. Ventricular arrhythmias occurred in less than 30% of the animals after tetrachloroethylene alone. In cats higher doses of tetrachloroethylene (40 mg/kg) produced acute pulmonary edema. Tetrachloroethylene (30–40 mg/kg) decreased left intraventricular $dP/dt_{(max)}$ in dogs, without significantly increasing left intraventricular end-diastolic pressure, although there was a transient decrease in arterial blood pressure that accompanied the early phase of myocardial depression. These results are being used as the basis for studies of the chronic effects of tetrachloroethylene on cardiac performance.

INTRODUCTION

Tetrachloroethylene (1,1,2,2-tetrachloroethene, perchloroethylene) is a widely used organic solvent that is becoming increasingly prevalent in the ambient air over urban-industrial areas (Bozzelli and Kebbekus, 1979). Dowty et al. (1975) demonstrated the presence of tetrachloroethylene both in the New Orleans drinking water and in the pooled plasma from a group of local residents. Water supplies of several other communities have also shown significant levels of tetrachloroethylene (Giger and Molnar-Kubica, 1978; Tucker, 1981). Dowty and his colleagues suggested that the lipophilic nature of the halogenated hydrocarbons and their occurrences in

The authors thank Mrs. Pramila Kumari for her assistance in performing the research.
This research was supported by a grant from the Princeton Institute of Environmental Medicine.
Requests for reprints should be sent to Duncan E. Hutcheon, Department of Pharmacology, College of Medicine and Dentistry of New Jersey, 100 Bergen Street, Newark, New Jersey 07103.

Journal of Toxicology and Environmental Health, 10:23-30, 1982

0098-4108/82/060023-08$2.25

the drinking water would allow them to accumulate in the blood and other tissues. The actual presence of tetrachloroethylene in wet tissue was established by McConnell et al. in 1975.

Chemically related halogenated hydrocarbons, such as methylchloroform and trichloroethylene, depress the myocardium and predispose the heart to the development of arrhythmias (Aviado et al., 1976; White and Carlson, 1979). Recently Abedin et al. (1980) described the occurrence of premature ventricular beats in a dry-cleaning worker exposed to tetrachloroethylene. Aside from this clinical report, however, little is known about the cardiotoxic effects of tetrachloroethylene. Experiments investigating the action of tetrachloroethylene on cardiac rhythm and performance were, therefore, designed.

METHOD

Five rabbits (3.4–4.1 kg) were anesthetized with urethane (1 g/kg). A tracheotomy was performed on each and a cannula was inserted into the external jugular vein to allow for intravenous injection of the test compounds.

Seven cats (1.9–3.0 kg) were anesthetized with sodium pentobarbital (30 mg/kg ip). A tracheotomy was performed on each cat to facilitate respiration. Actual respiration was regulated by a Harvard respirator pump. A polyethylene catheter was inserted into the external jugular vein for drug administration. A catheter (filled with saline containing 8 units/ml heparin) inserted into the carotid artery was used to measure arterial blood pressure in conjunction with a Statham transducer and a Grass polygraph.

Six mongrel dogs (18.5–27.5 kg) were anesthetized with sodium pentobarbital (30 mg/kg iv) and endotracheal intubations were performed to maintain respiration, which was regulated by a Palmer respiration pump. Arterial and left ventricular pressures were measured by means of Statham transducers connected to appropriately placed catheters and a DR-8 Electronics-for-Medicine recorder. The first derivative of the left ventricular pressure rise, $dP/dt_{(max)}$, was derived electronically and recorded along with Lead II of the electrocardiogram and the arterial blood pressure for each dog.

After the preparatory surgery, Lead II EKG, and blood pressure recording, various doses of epinephrine (0.25, 0.6, 1.0 μg/kg in rabbits; 5, 10, 15, 20 μg/kg in cats; and 2.5, 5.0, 10 μg/kg in dogs) were given to determine the nature and severity of the catecholamine-induced arrhythmias. Twenty minutes after this control period, the same dose of epinephrine just described was administered, followed by intravenous injection of tetrachloroethylene (5–10 mg/kg in rabbits, 10–40 mg/kg in cats, 5–20 mg/kg in dogs). This was followed by another injection of epinephrine. The tetrachloroethylene was dispersed in 0.05% Tween 80,

which by itself had no demonstrable cardiotoxicity, to provide a suspension suitable for injection. Tetrachloroethylene was injected intravenously primarily to avoid uncertain dosimetry, which is the result of administration by either the oral route or inhalation.

Plasma concentrations of tetrachloroethylene in rabbits were measured by gas chromatography following the injection of 10 mg/kg tetrachloroethylene into the external jugular vein. Blood samples were collected from the carotid artery at 0.5, 1.5, 15, 30, 60, 90, 120, and 180 min after injection. Blood samples were centrifuged at 4°C and the tetrachloroethylene was extracted from the plasma using *n*-pentane (Aldrich Chemical, Milwaukee, Wis.). Tetrachloroethylene analysis was performed using a gas chromatograph equipped with a ^{63}Ni electron capture detector (Tracor, Austin, Tex.).

RESULTS

In rabbits under urethane and in cats and dogs under pentobarbital anesthesia tetrachloroethylene was capable of producing ventricular arrhythmias and increasing the vulnerability of the myocardium to epinephrine-induced ventricular premature contractions, bigemini, and tachycardia.

Mean threshold doses of tetrachloroethylene and epinephrine for the production of arrhythmias are shown in Table 1. Rabbits under urethane were the most sensitive to the development of catecholamine-induced ventricular arrhythmias after exposure to tetrachloroethylene. As shown in Fig. 1, doses as low as 0.6 μg/kg epinephrine and 5 mg/kg tetrachloroethylene were capable of producing ventricular tachycardia in the rabbit heart. Tetrachloroethylene administered alone led to the development of ventricular premature beats in less than 30% of the experiments.

The plasma levels of tetrachloroethylene in three rabbits showed that, after administration of a dose of 10 mg/kg (the threshold dose for increasing the vulnerability of the ventricles to arrhythmias), the occurrence of increased ventricular ectopic activity corresponded to plasma levels between 2.2 and 3.6 μg/ml. These values were reached during the

TABLE 1. Threshold Doses (Mean ± SE) for Ventricular Arrhythmias

	N	Tetrachloroethylene (mg/kg)	Epinephrine[a] (μg/kg)
Cats	7	24.3 ± 8.4	13.6 ± 2.1
Rabbits	5	10.0 ± 3.5	0.7 ± 0.1
Dogs	6	13.3 ± 5.9	4.2 ± 0.5

[a]Dose after a threshold dose of TCE. Both compounds given intravenously.

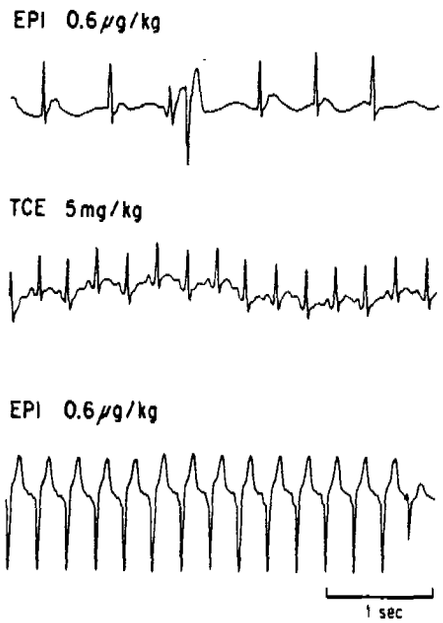

FIGURE 1. Epinephrine (EPI) induced ventricular tachycardia in the rabbit under urethane anesthesia after 5 mg/kg tetrachloroethylene (TCE) iv. Lead II EKG.

early alpha, or disposition phase, which had a $t_{1/2}$ of 3.8 min. Concentrations below those values, maintained during the more prolonged, dominant elimination phase ($t_{1/2}$ = 288 min), were not associated with any apparent increase in the vulnerability of the ventricles to arrhythmias.

The number of ectopic beats induced by epinephrine after the injection of tetrachloroethylene depended partly on the underlying heart rate. With baseline rates below 100/min, the average number of premature ventricular contractions triggered by epinephrine in the presence of tetrachloroethylene was 0.4/min and was not significantly different from that during the control period. With heart rates of 100 to 150/min, the average number of premature contractions induced by epinephrine was 28/min and, with heart rates above 150/min, the average number of ectopic beats was more than 32/min. The apparent protective influence of the slow cardiac rate on the occurrence of epinephrine-induced ventricular arrhythmias was presumably due to sympathetic underactivity rather than increased vagal activity. In the presence of tetrachloroethylene, vagotomy produced cardioacceleration without increasing the number of epinephrine-induced ventricular beats.

The effects of tetrachloroethylene on systemic arterial pressure, left intraventricular pressure, and the rate of pressure rise ($dP/dt_{(max)}$) were investigated in dogs under pentobarbital anesthesia. Doses of 20–40 mg/kg iv tetrachloroethylene produced significant depressions of $dP/dt_{(max)}$

TABLE 2. Effect of Tetrachloroethylene on Left Ventricular $dP/dt_{(max)}$ in Dogs

Dog	$dP/dt_{(max)}$ (% of control)		
	5 mg/kg tetrachloroethylene	20 mg/kg tetrachloroethylene	40 mg/kg tetrachloroethylene
1	62	89	50
2	113	94	78
3	84	48	52
4	97	86	78
5	99	83	70
6	78	67	50
Mean ± SE	88.9 ± 7.3	77.6 ± 7.1	63.1 ± 5.7

(Table 2). As shown in Fig. 2, a transient decrease in arterial blood pressure occurred after the injection of tetrachloroethylene, accompanied by a small rise in the left ventricular diastolic pressure. However, the hypotensive effect of tetrachloroethylene was short-lived in relation to the more persistent depression of dP/dt. In the absence of significant changes in the arterial blood pressure and heart rate, measurement of $dP/dt_{(max)}$ may serve as an index of myocardial contractility (Wallace et al., 1963). The evidence from this experiment indicates that doses as low as 20–40 mg/kg administered intravenously are capable of producing direct myocardial depression. The results are similar to those for 1,1,1-trichloroethane and trichloroethylene, which have also been observed to depress myocardial contractility under similar experimental conditions (Aviado, 1978; Herd et al., 1974).

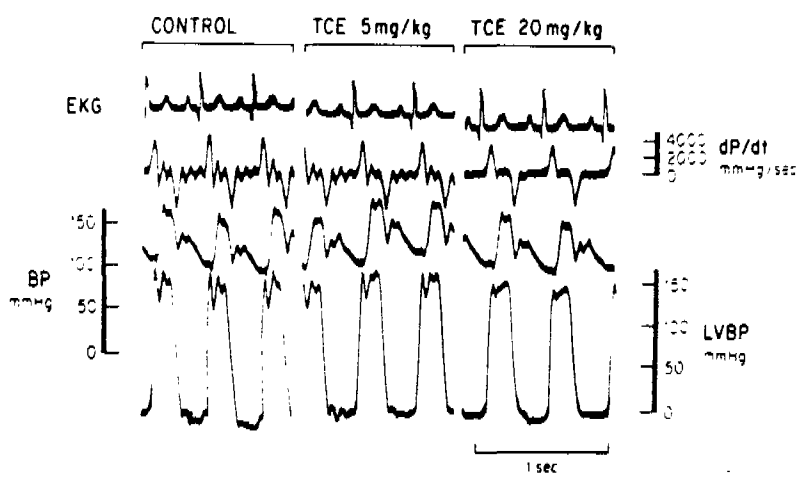

FIGURE 2. Effects of tetrachloroethylene (TCE) on left intraventricular pressure and dP/dt in the dog under pentobarbital anesthesia.

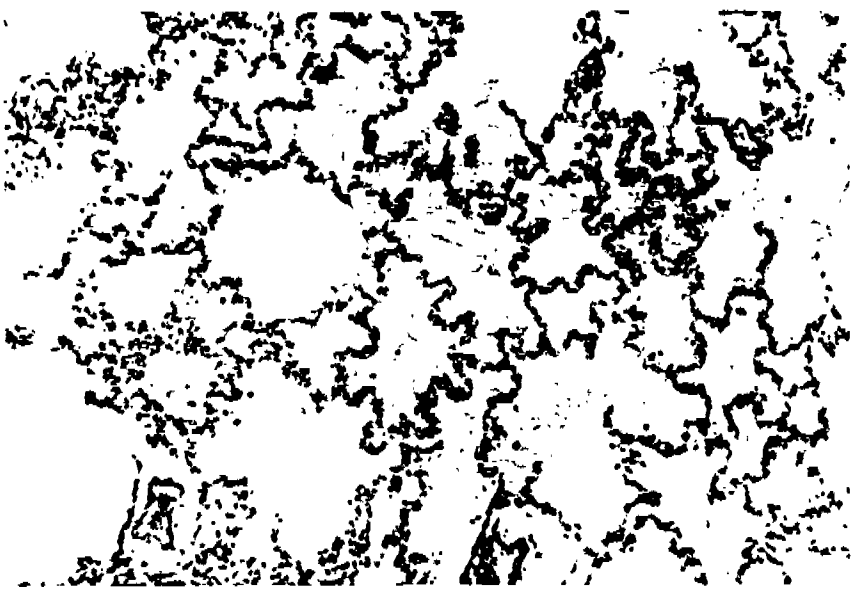

FIGURE 3. Microscopic section of lung showing acute pulmonary edema after 50 mg/kg iv tetrachloroethylene in the cat, X190.

The mean lethal dose of tetrachloroethylene in cats under pentobarbital anesthesia (± SE) was 81.4 ± 14.4 mg/kg iv. Acute pulmonary edema occurred as the first manifestation of toxicity after doses as low as 40 mg/kg (Fig. 3). EKG and blood pressure recordings demonstrate that acute pulmonary edema developed without any evidence of shock or clinically significant arterial or left ventricular diastolic pressure changes.

DISCUSSION AND CONCLUSIONS

The possibility of cardiac depression following exposure to tetrachloroethylene has been known as far back as 1933 (Christensen and Lynch, 1933). However, subsequent research on the toxicology of tetrachloroethylene has been limited to studies of its effects on the central nervous system (Rowe et al., 1952; Stewart et al., 1970), liver (Klaassen and Plaa, 1966), and kidney (Plaa and Larson, 1965). Tetrachloroethylene in the ambient air may lead to irritation of the eyes and symptoms of central nervous system dysfunction, but the clinical impression is that it does not produce severe organ injury. Stewart et al. (1970) set 100 ppm tetrachloroethylene in the inspired air as the maximum safe level. When given orally, tetrachloroethylene is generally considered to be safe, as evidenced by its use in the treatment of hookworm infestations of the intestine (Sharp, 1930).

The currently accepted view that tetrachloroethylene is not cardiotoxic

is supported by the results of the occupational study of Blair et al. (1979), who found no increase in the prevalence of deaths due to cardiovascular disease in laundry and dry-cleaning workers exposed to the solvent daily. Accidental and occupational exposure to tetrachloroethylene produces symptoms of central nervous system depression (Stewart, 1969) and liver injury (Coler and Rossmiller, 1953). Acute pulmonary edema may also occur in those exposed to high levels of tetrachloroethylene (Patel et al., 1977). Although x-rays have shown cardiac dilatation in such cases, the risk of myocardial depression and injury has generally not been appreciated.

The results of the present study demonstrate that tetrachloroethylene, like other organic solvents, is capable of depressing the myocardium and increasing the vulnerability of the ventricles to arrhythmias. The apparent absence of cardiotoxic symptoms in those exposed to tetrachloroethylene may therefore be due more to poor absorption rather than to pharmacologic inactivity.

Because tetrachloroethylene is only soluble in about 10,000 volumes of water, it is poorly absorbed when administered by inhalation or by the oral route. Breathing concentrations of 200 ppm in the inspired air for 2 h gave levels less than 30 ppm in the alveolar air (Fernandez et al., 1976). Intravenously, the lethal dose of tetrachloroethylene in dogs is about 80 mg/kg, whereas orally, 18 g/kg were well tolerated (Barsoum and Saad, 1934). Thus, absorption characteristics appear to be more important than intrinsic target organ toxicity in determining the overall safety of tetrachloroethylene at environmental levels of exposure.

REFERENCES

Abedin, A., Cook, Z. C., and Milberg, R. M. 1980. Cardiac toxicity of perchloroethylene (a dry cleaning agent). *South. Med. J.* 73:1081–1083.

Aviado, D. M., 1978. Physiological and biochemical responses to specific groups in inhalants: Concluding remarks. *Fed. Proc.* 37:2508–2509.

Aviado, D. H., Zakhari, S., Simaan, J. A., and Ulsamer, A. G. 1976. *Methylchloroform and Trichloroethylene in the Environment*, ed. L. Golberg. Cleveland, Ohio: CRC Press.

Barsoum, G. S. and Saad, K. 1934. Relative toxicity of the chlorine derivatives of the aliphatic series. *Q. J. Pharm. and Pharmacol.* 7:205–214.

Blair, A., Decoufle, P., and Grauman, D. 1979. Causes of death among laundry and dry cleaning workers. *Am. J. Public Health* 69:508–511.

Bozzelli, J. and Kebbekus, B. 1979. *Analysis of Selected Volatile Organic Substances in Ambient Air.* Trenton, N.J.: New Jersey Department of Environmental Protection.

Christensen, B. V. and Lynch, H. J. 1933. The effect of anthelmintics on the host. I. Tetrachloroethylene. II. Hexylresorcinol. *J. Pharmacol. Exp. Ther.* 48:311–316.

Coler, H. R. and Rossmiller, H. R. 1953. Tetrachloroethylene exposure in a small industry. *Arch. Ind. Hyg. Occup. Med.* 8:227–233.

Dowty, B., Carlisle, D., and Laseter, J. L. 1975. Halogenated hydrocarbons in New Orleans drinking water and blood plasma. *Science* 187:75–77.

Fernandez, J., Guberan, E., and Caperos, J. 1976. Experimental human exposure to tetrachloroethylene vapor and elimination in breath after inhalation. *Am. Ind. Hyg. Assoc. J.* 37:143–150.

Giger, W. and Molnar-Kubica, E. 1978. Tetrachloroethylene in contaminated ground and drinking waters. *Bull. Environ. Contam. Toxicol.* 19:475–480.

Herd, P. A., Lipsky, M., and Martin, H. F. 1974. Cardiovascular effects of 1,1,1-trichloroethane. *Arch. Environ. Health* 28:227–233.

Klaassen, C. D. and Plaa, G. L. 1966. Relative effects of various chlorinated hydrocarbons on liver and kidney function in mice. *Toxicol. Appl. Pharmacol.* 9:139–151.

McConnell, G., Furguson, D. M., and Pearson, C. R. 1975. Chlorinated hydrocarbons and the environment. *Endeavour* 34:13–18.

Patel, R., Janakiraman, N., and Towne, W. D. 1977. Pulmonary edema due to tetrachloroethylene. *Environ. Health Perspect.* 21:247–249.

Plaa, G. L. and Larson, R. E. 1965. Relative nephrotoxic properties of chlorinated methane, ethane, and ethylene derivatives in mice. *Toxicol. Appl. Pharmacol.* 7:37–44.

Rowe, V. K., McCollister, D. D., Spencer, H. C., Adams, E. M., and Irish, D. D. 1952. Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. *Arch. Ind. Hyg. Occup. Med.* 5:566–579.

Sharp, E. A. 1930. The relation of toxicity to dosage of tetrachloroethylene (C_2Cl_4). *J. Trop. Med. Hyg.* 33:336–339.

Stewart, R. D. 1969. Acute tetrachloroethylene intoxication. *J. Am. Med. Assoc.* 208:1490–1492.

Stewart, R. D., Baretta, E. D., Dodd, H. C., and Torkelson, T. R. 1970. Experimental human exposure to tetrachloroethylene. *Arch. Environ. Health* 20:224–229.

Tucker, R. K. 1981. *Reports on Ground Water Quality in New Jersey and Investigation of Toxic Contaminants.* Trenton, N.J.: Office of Cancer and Toxic Substances Research, New Jersey Department of Environmental Protection.

Wallace, A. G., Skinner, N. S., Jr., and Mitchell, J. H. 1963. Hemodynamic determinants of the maximal rate of rise of left ventricular pressure. *Am. J. Physiol.* 205:30–36.

White, J. F. and Carlson, G. P. 1979. Influence of alterations in drug metabolism on spontaneous and epinephrine-induced cardiac arrhythmias in animals exposed to trichloroethylene. *Toxicol. Appl. Pharmacol.* 47:515–527.

Received September 17, 1981
Accepted December 5, 1981