CASE REPORT

Antonio Tombolini,[1] *M.D. and Mariano Cingolani,*[1] *M.D.*

Fatal Accidental Ingestion of Carbon Tetrachloride: A Postmortem Distribution Study

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ABSTRACT: This paper reports a fatality involving a 75-year-old white male, who ingested an unknown quantity of carbon tetrachloride (CCl_4)—a toxic agent able to induce central nervous system depression and severe renal and hepatic damage—and who died after two days of intensive care. The analytical assessment of CCl_4 concentration was performed on several biological fluids and tissues employing gas chromatography-flame ionization detection (GC-FID) head space method. Both *urine* (328.5 mg/L) and *bile* (169.8 mg/L) had high concentrations of CCl_4, proving that the chemical undergoes extensive urinary and biliary excretion. In accordance with the high clearance power of lungs, *systemic venous blood,* (143.4 mg/L) had a concentration of CCl_4 almost two and half times greater than in *arterial blood* (57.5 mg/L), representing the best specimen to correlate CCl_4 blood concentration with the deep of narcosis. *Vitreous humor,* (170.5 mg/L) concentration of CCl_4 proves the capability of the chemical to enter eyes and its relatively slow release into the systemic blood. *Pancreas* (657.9 mg/kg), *brain* (243 mg/kg) and *testis* (237.3 mg/kg) have great affinity for CCl_4. The concentrations of the chemical in brain are cortex: 243.2 mg/kg, basal ganglia: 216.1 mg/kg, medulla oblongata: 243.3 mg/kg and cerebellum: 175.3 mg/kg. As the depth of narcosis is correlated with CCl_4 concentration, brain represents the most suitable tissue for toxicologic analysis. Lower concentrations of the chemical are found in *lungs* (127.3 mg/kg), *kidneys* (150.5 mg/kg), *muscle* (71.1 mg/kg), *myocardium* (78.5 mg/kg) and *spleen* (68.3 mg/kg). *Liver* (58.6 mg/Kg), a frequently analyzed tissue in forensic toxicology, shows the lowest concentration.

KEYWORDS: forensic science, pathology, toxicology, forensic pathology, forensic toxicology, carbon tetrachloride—poisoning—oral ingestion—distribution, fatality, accidental death

Carbon tetrachloride (tetrachloromethane, CCl_4) is a volatile chemical agent with toxic property. It has been employed as a dry cleaner, a fire extinguisher, a fumigant for grain, a degreaser of machine parts and electrical equipment, a solvent in the rubber and paint industries, a constituent of soap solutions in the textile industry and in the quartz crystal industry, in the manufacture of the refrigerant Freon 12 and of D.D.T., in the extraction of oils and fats from plants and animal substances (1). It has been used also as an antihelmintic drug (2).

The high toxicity of the chemical agent resulted in discontinuance of therapeutic use and every day and industrial employment have been reduced.

Several cases of acute poisoning subsequent to inhalation (3,4) or ingestion (5) of CCl_4 have been reported. In an adult human being, the mean lethal dose by mouth appears to lie between 5 and 10 mL. However, as little as 2 mL, has caused death (6,7).

The principal toxic effects are central nervous system depression and cellular necrosis in liver and kidneys. Death may be due to either one.

The immediate effects of acute intoxication are narcosis and irritation of mucous membrane (conjunctivitis, vomiting, diarrhea and coughing). The rapid onset of narcosis almost ensures that the acute narcotic effect of CCl_4 is due to the chemical agent itself and not metabolites (8). However, the predominant effects of severe, not immediately fatal, injury are those related to a hepatorenal syndrome, occurring after a latent period of two to eight days. Liver and renal toxicity is due to the CCl_4 metabolites produced in the liver (8).

Although there are many exceptions, nervous symptoms appear to be predominant in inhalation exposures, whereas gastrointestinal and hepatorenal injuries are more prominent after ingestion (3,9,10). Symptoms develop slower after ingestion (latency 24 to 36 hours) than after inhalation (latency usually a few minutes).

Necrosis of liver cells (especially those in the central portion of each lobule) represents the principal histologic lesion, together with fatty infiltration. In the kidneys, fatty degeneration and necrosis of the renal tubular epithelium may be extensive.

CCl_4 is readily absorbed by the lungs. It is also well absorbed by the intestinal tract. The rate of absorption differs with the species, but when injected into the small intestine CCl_4 appears in the expired air after a few minutes, reaches a maximum concentration in approximately one hour, and then continues to be excreted at a slow rate for considerable time (11).

CCl_4 is metabolized in the liver by the cytochrome *P-450-dependent mixed-function oxidase* to only a slight extent (8).

Excretion of the parent compound is almost entirely through the lungs; this is due to its extreme volatility (boiling point: 76,8°C). However a small amount is also excreted in urine and feces.

Literature review revealed three studies on the distribution of the CCl_4 in the body. The oldest one (11) reports a very high concentration of CCl_4 in the bone marrow. In the liver, pancreas

[1]Medical Examiners of Cattedre di Medicina Legale, University of Ancona, Ospedale Regionale 1-60020 Ancona, Italy.

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and brain the concentration was about one fifth of that in the bone marrow. McCollister et al. (12) found the highest concentration of radioactive CCl_4 in the fat. Both of these studies, regardless the analytical technique employed, examined CCl_4 distribution in animals only.

The third study (13) is noteworthy as it concerns a human adult who died seven days after a single inhalation exposure to CCl_4.

No studies have been found about the distribution pattern of CCl_4 after oral ingestion. The aim of this study is to determine the distribution pattern of CCl_4 in the human body in a fatal case due to oral ingestion of the chemical.

Case History

The decedent was a 75-year-old white male. He accidentally ingested an unknown quantity of CCl_4 from an open sparkling wine bottle stored in the cellar. His relatives hospitalized him immediately because of persistent drowsiness and severe diarrhea. At admission he was unconscious and cyanotic. Laboratory testing revealed a slightly increased transaminase (SGOT 82 U/L) and creatinine (1.29 mg/dL) serum level. During the following hours transaminasemia and creatininemia raised rapidly. After 12 hours SGOT 1191 U/L, creatinine 1.60 mg/dL. The patient became icteric (bilirubinemia 8.12 mg/dL). After two days of intensive care he died due to hepatic and renal failure. The external examination and the autopsy escluded causes of death not related to the intoxication. Organs weighted as follows: brain 1280 g, heart 660 g, right lung 475 g, left lung 480 g, liver 1620 g, spleen 210 g, pancreas 105 g, right kidney 180 g, left kidney 135 g. Death was attributed to massive pulmonary edema and cardiac arrest due to severe hepatic and renal failure. The toxicologic screening for basic, acid and neutral drugs were with negative results. The histologic findings showed a massive pulmonary edema and severe necrosis of centrolobular liver cells and tubular renal cells.

Toxicologic Analysis

Sampling and Storage

Biological fluids and tissues listed in Table 1 were collected during autopsy. One gram of tissue was mechanically homogenized in 2 mL of distilled water. One mL of each biological fluid and tissue homogenate were sealed immediately in suitable vials. Several vials for each specimen were prepared in order to repeat the analysis at least three times. All the vials were stored at −20°C prior to the analysis.

TABLE 1—*CCl_4 concentration in biological fluids and tissues.*

Specimen	CCl_4 concentration (mg/L (kg))
Urine	328.5
Vitreous humor	170.5
Bile	169.8
Venous blood	143.4
Arterious blood	57.5
Pancreas	657.9
Brain (medulla oblongata)	243.3
Brain (cortex)	243.2
Testis	237.3
Brain (basal ganglia)	216.1
Cerebellum	175.3
Kidney	150.5
Lung	127.3
Myocardium	78.5
Muscle	71.1
Spleen	68.3
Liver	58.6

Preparation of the Sample

The head-space method was employed. Each vial was kept in a thermostated-bath at a temperature of 80°C for two hours prior to analysis. One mL of the vapor phase was injected into the column.

Instrumentation

The toxicologic analysis was performed using a Carlo Erba Gas chromatograph equipped with a Carbowax 20 M on Carbopak B 60–80 mesh 2 m × 2 mm I.D. packed column and a flame ionization detector (FID). The analysis was performed using the following parameters: carrier gas flow (N_2): 30 mL/min, oven temperature: 90°C, injector and detector temperature: 110°C.

Quantitation

The analysis of each sample was done in triplicate. The final value was the mean of the peak areas obtained in each run. To calculate the concentration of the CCl_4 in the sample, external standard at five different concentrations (50 mg/L, 100 mg/L, 150 mg/L, 200 mg/L and 600 mg/L) was prepared and submitted to analysis like other samples. The external standard calibration curve is showed in Fig. 1.

Results and Discussion

The results of the toxicologic analyses are listed in Table 1. They give the postmortem distribution pattern of CCl_4 in the body after ingestion. They allow for some observations about the kinetics of the chemical in the body and the suitability of different biological fluids and tissues for forensic purposes in fatal cases due to ingestion of CCl_4 with a few days survival.

Among the biological fluids analyzed, *urine* has the highest concentration of CCl_4 three times greater than systemic venous blood. This shows that the absorption phase is ended 48 hours

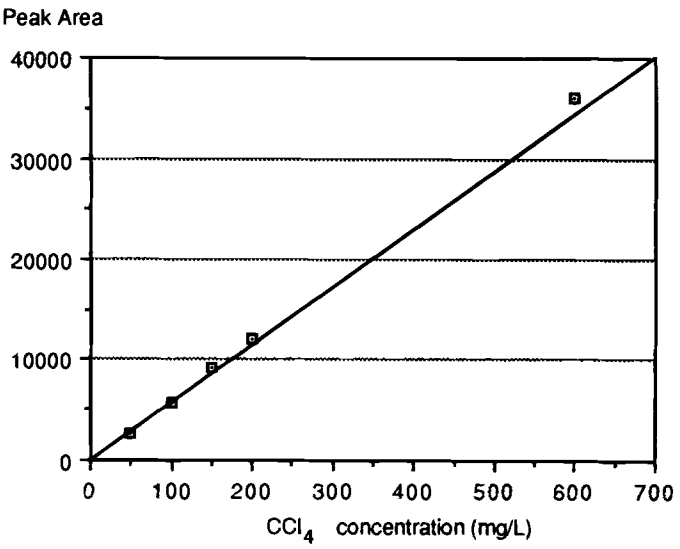

FIG. 1—*Calibration curve of the external standards (50, 100, 150, 200 and 600 mg/L).*

after ingestion (the subject survived for two days), the chemical undergoing extensive excretion in urine. Urine appears to be the most suitable biological fluid for toxicologic analysis of CCl_4 in fatal cases in which death takes place several days after ingestion.

The concentration of CCl_4 in the *systemic venous blood* is almost two and half times greater than that in the arterial blood. This may be due to the high clearance ability of the lungs of this volatile chemical. The acute narcotic effect of CCl_4 is due to the chemical agent itself and not metabolites. Thus, in order to correlate the depth of narcosis with the CCl_4 blood concentration, it is advisable to assess the concentration of the chemical in the systemic venous blood avoiding any contamination and dilution with the arterial blood.

Vitreous humor showed a concentration of CCl_4 slightly greater than systemic venous blood. This shows the capability of the chemical to enter eyes and its relatively slow release into systemic blood. As vitreous humor is less subject to the bacterial contamination and consequently postmortem putrefaction than other biological fluids, it represents a suitable sample for toxicological analysis.

An almost equal concentration of CCl_4 is found in the *bile*. This proves that bile is an important route of excretion and consequently a biological fluid to be collected in cases of suspected CCl_4 intoxications.

Among analyzed tissues, we found a very high concentration of CCl_4 in the *pancreas*. We cannot find a pharmacokinetics reason to explain such a high affinity. However, other studies also include pancreas among tissues with a high content of CCl_4 (11).

Brain and *testis* have a high affinity for CCl_4. The concentration of the chemical is almost independent from the brain zone of sampling; only the cerebellum has a lower concentration of CCl_4. The central nervous system depression is due to the parent compound and not metabolites (8). For this reason, brain represents the most suitable tissue to correlate CCl_4 concentration with the depth of central nervous system depression.

Lungs and *kidney* show an almost equal concentration of the chemical but less than brain. Lower levels of the chemical are in muscle, myocardium and spleen. According to the data of Krobenke and Pribilla (13), the concentration in muscle (46 mg/kg) is higher than in lungs (39 mg/kg) and kidney (32 mg/kg). This can be due to the fact that in the case reported by these authors, the subject survived seven days so that the chemical had more time to distribute widely in the body.

Liver, a frequently analyzed tissue in forensic toxicology, shows the lowest concentration among examined tissues. This is in contrast to the data of Krobenke and Pribilla (13), in which the liver (142 mg/kg) has a higher concentration than kidney or lungs. This could be explained by the different routes of entry of the chemical into the body. In case of oral ingestion the liver is the first organ to receive the blood flow and is subjected to a sudden raise in concentration of CCl_4 during the absorption phase. This results in rapid metabolism of the parent molecule, causing massive necrosis of liver cells due to metabolite accumulation. This massive necrosis could alter the enzymatic pattern of the liver (14,15) resulting in a decreased affinity of the necrotic liver cells for CCl_4. In case of inhalation, CCl_4 distributes slowly in the body and in the liver so that cellular damage is less severe and the hepatic cells don't lose their affinity. This is consistent with the clinical picture of CCl_4 acute intoxication in which nervous symptoms are said to be predominant in inhalation exposures, whereas gastrointestinal and hepatorenal injuries are more prominent after ingestion.

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Address requests for reprints or additional information to
Antonio Tombolini, MD
Cattedre di Medicina legale
Ospedale regionale di Torrette
I-60020, Ancona, Italy