

Carbon Disulfide Neurotoxicity: Taiwan Experience

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Abstract- Carbon disulfide (CS₂) intoxication may induce peripheral neuropathy, encephalopathy, and cardiovascular diseases. In our studies, abnormalities of the peripheral nerves including clinical symptoms and electrophysiological findings were still present 3 years after cessation of CS₂ exposure. The data indicate that CS₂ neuropathy may persist for a period of time. The involvement of central nervous system may continue even longer. Brain magnetic resonance images usually show multiple high signal intensities in the basal ganglia and subcortical white matter suggesting a vascular event particularly in the small vessels. In addition, a patient with diffuse demyelination in the cerebral hemispheres also showed a diffuse decrease of regional cerebral blood flow indicating a microangiopathy. Therefore, CS₂ exposure should be considered as a risk factor for strokes and one of the causes for diffuse leucoencephalopathy. Because CS₂ may induce parkinsonian features, a differential diagnosis between CS₂ parkinsonism and idiopathic parkinsonism is important. In our study, dopamine transporter with ^{99m}Tc-TRODAT-1 brain single photon emission computed tomography showed a normal uptake in the corpus striatum. The data suggest a normal presynaptic dopaminergic pathway function and provide useful information in differentiation. The involvement of cardiovascular systems may be due to thrombotic effects rather than atherogenic effects. In addition, absorption of CS₂ through skin is also significant particularly in workers with skin lesions.

Key Words: Carbon disulfide, Neurotoxicity, Peripheral neuropathy, Encephalopathy, Parkinsonism, Stroke

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INTRODUCTION

Carbon disulfide (CS₂) is a colorless, liquid organic solvent at room temperature with an odour of decaying cabbage. In its pure state, it has a sweet, pleasing and ethereal odour. CS₂ is volatile and flammable with a boiling point of 46.5°C. It is highly soluble in blood and fat and moderately soluble in urine and water (2.0 g/L at

20°C). In human and experimental studies, CS₂ is easily absorbed via inhalation, oral or skin routes and is distributed throughout the body, due to its affinity to lipid-rich tissues and organs. Inhalation of CS₂ may reach an apparent steady state within 1-2 hours. The absorbed CS₂ is concentrated in the red cells. In addition, absorption of CS₂ through the skin is also significant amounting to about 17.5 mg CS₂ after immersion of a hand for

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one hour in a washing bath in a viscose rayon plant⁽¹⁻³⁾.

CS₂ can be readily distributed to the brain and the liver and metabolized by cytochrome P-450. Three metabolites are found by the thin layer chromatography including thiocarbamide, 2-mercapto-2-thiazolinone-5 and 2-thiothiazolidine-4-carboxylic acid (TTCA). Among them, TTCA is the most important metabolite via conjugation with glutathion in the body. The elimination of absorbed CS₂ by exhalation varies from 10% to 30% within one hour. CS₂ level rapidly declines in the blood with a terminal half life of 55 minutes, and less than 10% of CS₂ is excreted unchanged in the urine. Because of its specificity and sensitivity, TTCA in urine has been considered as a biomarker of CS₂ exposure. The current biological exposure index is 5 mg/g creatinine (Cr).

The current threshold limit value (TLV) for the eight-hour Time-Weighted Average (TWA) concentration of CS₂ is 10 ppm as recommended by the American Conference of Governmental Industrial Hygienists (ACGIH). The current permissible exposure limit (PEL) is 4 ppm and TWA (10 hr) is 1 ppm, with a Short-Term Exposure Limit (STEL) at 10 ppm by the US National Institute for Occupational Safety and Health (NIOSH). The Occupational, Safety and Health Administration (OSHA) in the US final rule limits are the PEL TWA (8h) of 20 ppm, and STEL of 12 ppm. In addition, in view of its risks to reproduction, World Health Organization (WHO) has suggested a TWA of 0.96 ppm for women and 3.2 ppm for men in occupational exposure⁽⁴⁻⁶⁾. In Taiwan, a PEL of 20 ppm was suggested by Taiwan OSHA.

CS₂ was first used as a phosphorus solvent in match manufacture in 1851, and then widely used in the vulcanization of rubber and in the synthesis of carbon tetrachloride and the manufacture of cellophane, plywood, adhesive, and various oil products, lacquers and thinners. In the twentieth century, the major industrial application has involved in the viscose rayon manufactures.

CS₂ was the first industrial solvent to be considered as a neurotoxic agent in 1856. There are many reports concerning its toxicity particularly in the peripheral and central nervous systems, cardiovascular system, ophthalmological system, and even the reproductive system⁽⁷⁾.

CARBON DISULFIDE INTOXICATION

Acute exposure of more than 1,000 ppm of CS₂ may cause narcosis, toxic psychoses with delirium, excitability, seizures and mental impairments. Exposure to CS₂ concentrations of several hundreds ppm for several days may induce symptoms of headache, dizziness, vomiting and local irritation. Chronic exposure or repeated low dose exposure to CS₂ may induce polyneuropathy, parkinsonism, including cogwheel rigidity, decreased association movements, and intention tremor, and neuropsychological symptoms such as dizziness, headache, nausea, vomiting, sleep disturbance, depression, decreased concentration, and decreased potency⁽⁸⁻¹⁵⁾.

Experience in Taiwan

In Taiwan, neurological manifestations from chronic exposure to CS₂ have also been reported in viscose rayon workers since 1992⁽¹⁶⁾. Nine (5.5%) out of 163 workers developed overt polyneuropathy. The estimated 8-hour time TWA concentrations of CS₂ were around 40-67 ppm in the fiber cutting areas. The occurrence of polyneuropathy was generally correlated with the degree of exposure to CS₂. In addition, these workers also experienced chronic encephalopathy in the follow-up periods⁽¹⁷⁾.

Effects on the peripheral nervous system

Peripheral neuropathy induced by CS₂ is relatively mild including distal muscle weakness and paresthesia. There are a glove and stocking-like diminished sensation in touch, pin-prick, temperature and position sense, muscle weakness particularly in distal legs, and reduced tendon reflexes⁽¹⁸⁻²⁴⁾. Electrophysiological studies may show a reduction in amplitudes of compound muscle action potentials and sensory nerve action potentials, a prolongation of distal latencies, and a mild slowing of both motor and sensory nerve conduction velocities. The severity of peripheral neuropathy is generally correlated with the level of CS₂ exposure⁽¹⁶⁾.

The pathological studies on human peripheral nerves are unfortunately few^(9,10). In our study, sural nerve biopsy performed 2 years after cessation of CS₂ exposure revealed a decrease of fiber density, relative loss of large

myelinated fibers, and degeneration of both axon and myelin⁽²⁵⁾. In animal studies, light microscopic examination revealed multifocal axonal swelling in the paranodal regions and secondary demyelination. Electron microscopic examination revealed an accumulation of 10 nm neurofilaments leading to blockage of axoplasmal flow and secondary demyelination⁽²⁶⁻²⁹⁾. These findings are very similar to those with n-hexane intoxication or acrylamide poisoning⁽³⁰⁻³³⁾.

Only a few electrophysiological studies have shown the long-term effect of peripheral nerve damage after cessation of CS2 exposure⁽²⁴⁾. Either good improvement, partial improvement, or permanent damage has been reported^(8,24). However, long term prognosis and clinical features of the patients were not described. In our recent study, although neurological symptoms were improved, decreased muscle strength, sensory impairment and hyporeflexia were still present 3 years after cessation of CS2 exposure⁽³⁴⁾. The improvement of peripheral nerves either by serial nerve conduction studies or by sural nerve pathological studies was not observed. The data suggest that damage to the peripheral nervous system might persist for a long period of time.

Effects on the central nervous system (CNS)

With subacute exposure for few months, symptoms of manic-depressive psychosis, hallucinosis and suicidal attempt may appear similar to those with acute manganese toxicity⁽³⁵⁻⁴²⁾. The clinical features included nightmares, insomnia, mood fluctuation, excessive sexual behavior, paranoia, and slurred speech. Subsequently, depression was accompanied by tremor, incoordination, ataxia and memory impairment. Following long-term CS2 low dose exposure, polyneuropathy, parkinsonism with cogwheel rigidity, bradykinesia, and resting tremor, cerebellar ataxia, and pyramidal tract symptoms may appear^(1,8-13,35-40).

In most patients, onset of CNS manifestations is insidious and the course is slowly progressive. In some patients, onset of symptoms may be acute suggesting a vascular event⁽¹⁷⁾. In our previous study, 4 out of 9 patients also developed chronic encephalopathy with stroke-like episodes^(17,43).

In few studies with brain computed tomography

(CT), low density lesions were found in the basal ganglia, and the subcortical white matter, indicating possible cerebral infarctions^(35,36,44). In our studies, brain magnetic resonance images (MRI) revealed multiple high-signal intensity lesions in the basal ganglia and the subcortical white matter on T2-weighted images⁽¹⁷⁾. The data from clinical and neuroimaging studies seem to support the view that CS2 encephalopathy was vascular in origin⁽⁴³⁻⁴⁶⁾. In addition to multiple lacunar infarctions in the subcortical white matter, the basal ganglion and even the pons, intracranial large vessels had a normal caliber suggesting a small vessel disease⁽⁴³⁾. Brain single photon emission computed tomography (SPECT) with xenon-133 has showed a tendency towards focal blood flow disturbances in workers with long term exposure⁽³⁷⁾. However, some patients may also have diffuse white matter lesions indicating central demyelination⁽¹¹⁾. Our brain CT perfusion study in a patient with diffuse demyelination also demonstrated a diffuse decrease of regional blood flow and prolonged regional mean transit time in the subcortical white matter⁽⁴⁷⁾. Thus, the reduced regional cerebral blood flow in the brain CT perfusion might represent a microangiopathy, which could subsequently induce central demyelination in the brain MRI. From the above data, CS2 exposure may be considered a risk factor for stroke. Furthermore, CS2 poisoning should be considered as a cause of chronic leucoencephalopathy.

Differences between CS2 parkinsonism and idiopathic parkinsonism

CS2 may induce parkinsonian features consisting of stooped posture, hypomimia, monotonous speech, bradykinesia, cogwheel rigidity, slow gait and decreased association movements⁽¹¹⁻¹³⁾. Therefore, differential diagnosis between CS2 parkinsonism and idiopathic parkinsonism becomes a diagnostic challenge. However, close examinations of the clinical features in CS2 parkinsonism patients reveal a relatively young age, more frequent mental impairment, rare bradykinesia, frequent coordination deficits and a poor response to antiparkinsonian agents in addition to prevalent polyneuropathy and cerebellar dysfunction.

One recent report with positron emission tomogra-

phy described a severe reduction in 6-fluorodopa uptake in the putamen and the caudate after long term CS₂ exposure⁽⁴⁸⁾. The data indicate a presynaptic dopaminergic damage of the nigrostriatal pathway. However, he did not respond to levodopa treatment. The exact mechanism is not provided. Our recent dopamine transporter (DAT) SPECT study with ^{99m}Tc-TRODAT-1 showed a normal uptake in the basal ganglia⁽⁴⁹⁾. The data indicate a normal presynaptic dopaminergic pathway. The result may provide a useful information in differentiation between CS₂ induced parkinsonism and idiopathic parkinsonism.

Neuropathological mechanisms

The neuropathological mechanisms of CS₂ parkinsonism remain unclear. In some human neuropathological studies, there were diffuse involvement of the cortical neurons and swelling of the endothelium with perivascular infiltration by lymphocytes and lipid deposits in the vessel walls⁽⁹⁾. In experimental monkey studies, degeneration of the globus pallidum and the zona reticulata of the substantia nigra were noted in addition to other neuronal changes in the cortex, the cerebellum, and even the medulla oblongata⁽³⁹⁾. In another study on manganese intoxication, a normal DAT with ^{99m}Tc-TRODAT-1 SPECT but damage to the globus pallidum were observed⁽⁵⁰⁾. Therefore, damage to the globus pallidum downstream to the dopaminergic system may be a plausible mechanism in CS₂ induced parkinsonism.

Effects on the cardiovascular system

Long-term exposure to CS₂ may lead to an increase in mortality due to coronary artery diseases⁽⁵¹⁻⁵⁷⁾. A direct cardiotoxic or thrombotic effect rather than an atherogenic effect has been observed^(55,56). In long-term exposure to CS₂, bradycardia, tachycardia, and/or other arrhythmias have been suggested^(51,53). Electrocardiographic studies showed either non-specific changes or ischemic abnormalities. Laboratory studies revealed an increase in β -lipoprotein and total cholesterol, in addition to an increase in triglyceride and β -low density lipoprotein cholesterol and a decrease in high density lipoprotein cholesterol⁽⁵⁸⁻⁶⁰⁾. Besides, an exposure to high CS₂ concentration is significantly associated with an increased risk for coronary heart diseases.

The precise mechanisms of CS₂ induced cardiovascular abnormalities are still unclear, although some hypotheses have been proposed including changes in lipid metabolism and fibrinolytic activities, advanced lipid infiltration, acceleration of atherosclerosis, and sub-clinical hypothyroidism⁽⁵³⁾. In addition, CS₂ may interfere with normal inhibition of elastase activities resulting in excessive elastase activity with disruption of vascular walls and formation of aneurysms. CS₂ has also been proposed to decrease fibrolytic activity and enhance thrombosis^(53,59). Animal studies have showed that CS₂ has an adverse effect on the cardiac muscle fibers and on the wall of the aorta⁽⁶⁰⁾.

Biological monitoring of TTCA

TTCA in urine has been generally applied as a useful biomarker of CS₂ exposure⁽⁶¹⁻⁶⁵⁾. The level of urinary TTCA can reflect the exposure of the day⁽⁶³⁻⁶⁵⁾. Shih et al.⁽⁶⁶⁾ also found that accumulation for occupational exposure to CS₂ was exposure-magnitude-dependant. From a recent study, the half-life for urine TTCA among CS₂-exposed workers was estimated to be 8.3 hours⁽⁶⁵⁾. There was a linear correlation between TTCA values in the urine and the CS₂ values in the air. In addition, dermal absorption of CS₂ for workers with skin diseases was significantly greater than those without⁽⁶³⁾. The data indicate that skin absorption of CS₂ in the occupational settings is a concern. Workers with susceptible skins should be warned and required to wear protective clothing⁽⁶⁷⁾.

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