Polyneuropathy Induced by n-Hexane Intoxication in Taiwan

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Abstract- n-Hexane and methyl n-butyl ketone share a common metabolite, 2,5-hexanedione, a potent neurotoxin. Neurotoxic effects to both peripheral and central nervous systems may occur after occupational exposure or recreational abuse of n-hexane. Initial clinical manifestations include numbness and tingling sensation in the toes and fingers, followed by progressive weakness and areflexia, particularly in the distal limbs.

Chronic low-dose n-hexane exposure, often observed in industrial workers, apparently causes axonal loss with sensory impairment. Subacute high-dose n-hexane exposure, often observed in glue-sniffers, can cause axonal swelling and secondary demyelination with muscle wasting and weakness.

Electrophysiological studies demonstrate prominent prolongation of distal latencies, slowing of nerve conduction velocities, and conduction block with temporal dispersion particularly in severely intoxicated patients. Pathological hallmarks include giant axonal swelling with secondary demyelination and relative loss of large myelinated fibers. Giant axons are accumulated by 10nm neurofilaments. The clinical course tends to be biphasic with “coasting” for 2-3 months, followed by a slow recovery for about 1-2 years after cessation of exposure to n-hexane. Prognosis is usually favorable. Severely affected patients may develop sequelae of muscle wasting, foot drop, and spasticity. Increased awareness of the n-hexane neurotoxicity in industrial workers and glue sniffers as well as use of safe solvents and adequate ventilation systems are important for preventing n-hexane toxicity.

Key Words: n-Hexane, Methyl-n-butyl-ketone, γ-Diketone, Polyneuropathy, Electrophysiology, Giant axon, Demyelination

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INTRODUCTION

The alkane n-Hexane, a 6-carbon aliphatic hydrocarbon (CnH2n+2), is a common component in lacquers, glues and glue thinner, and is widely used in numerous industrial processes\(^1\).\(^2\). The chemical is a colourless volatile organic solvent at room temperature with a characteristic odour and is known to be a potent neurotoxin. Approximately 80-90% of n-hexane can be absorbed by inhalation and then is distributed to lipid-rich tissues and organs such as the brain, peripheral nerves, liver, spleen, kidneys and adrenal glands. The

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alkane n-hexane and methyl n-butyl ketone (MnBK) are structurally similar and can be metabolized to the active neurotoxin γ-diketone, 2,5-hexanedione (2,5-HD), although only a small fraction of n-hexane can be metabolized to 2,5-HD (3-6). Whereas MnBK is moderately water soluble and has an acetone-like odour, 2,5-HD is completely miscible with water. The MnBK can be absorbed by inhalation as well as via dermal and oral routes while 2,5-HD is absorbed following dermal application in experimental animals. The urinary concentration of 2,5-HD is apparently comparable to that of airborne n-hexane (6). Urinary 2,5-HD assays are complex but reliable biomarkers.

INDUSTRIAL USE AND SAFETY LEVELS

Industrial application of n-hexane include production of glues, cements, inks and adhesives, painting and coating products, laminating plastics, lacquers, press proofing chemicals and cleaning agents. The chemical is also used for manufacturing and processing leather and furniture, as well as vulcanization of rubber and in dilution and extraction solvents in chemical laboratories (6-8). n-Hexane is also used to extract vegetable oils for human consumption and as a benzene substitute in solvent applications (6). MnBK is a widely used as monoketonic solvent, and small amounts of 2,5-HD are used as a precursor for various heterocyclic systems in synthetic organic chemistry (6).

The safety level of n-hexane, including the threshold limit value (TLV)-time weighted average, is 50 ppm (180 mg/m³) in the air according to the American Conference of Governmental Industrial Hygienists (ACGIH) (10). The TLV for MnBK is 5 ppm (20 mg/m³) in the air, and permissible exposure level (PEL) is 100 ppm. The U.S. Occupational Safety and Health Administration (OSHA) PELs are 500 ppm for n-hexane and 1 ppm for MnBK (11).

OUTBREAK OF N-HEXANE POLYNEUROPATHY

An outbreak of n-hexane-induced polyneuropathy due to occupational exposure was first reported in 1964 in poorly ventilated polyethylene laminating plants (12). Subsequently, this neurotoxic disease also occurred in pharmaceutical and vinyl sandal manufacturing plants, as well as in furniture, printing, and shoe manufacturing facilities between 1966 and 1980 (13-25). Awareness of this neurotoxic agent and implementation of preventive measures have increased in most industrialized countries, but occasional outbreaks continue (26-29).

Because of the euphoric effects of n-hexane, teenagers are easily addicted to glue-sniffing (28,29). Therefore glue-sniffing neuropathy, also known as huffer neuropathy, after habitual inhalation of glue vapors became a familiar neurological disease in 1970-1985 (30-37). The most notorious outbreak of MnBK-induced polyneuropathy was reported in Ohio in 1973 (38). The MnBK has greater neurotoxic potential than n-hexane. Additionally, despite its lack of neurotoxic effect, another organic solvent, methyl-ethyl-ketone (MEK) is known to potentiate the neurotoxic effect (6-8).

N-HEXANE POLYNEUROPATHY IN TAIWAN

Two outbreaks of n-hexane induced polyneuropathy have occurred in Taiwan (26,39,40). In December, 1983, a 16-year-old young boy working in a press-proofing plant visited the author in Chang Gung Memorial Hospital due to muscle weakness and distal limb numbness for approximately 1 year. Moderate muscle weakness and intrinsic muscle wasting was noted in both hands and feet, with a glove and stocking pattern of sensory impairment and generalized areflexia (39). Nerve conduction studies revealed significantly reduced nerve conduction velocities and prolonged distal latencies in all the nerves, particularly in the lower extremities. Therefore, the diagnosis of polyneuropathy was established. The young victim of polyneuropathy led to an extensive investigation among 54 workers from 16 press proofing factories in Taipei (26). Fifteen workers had overt polyneuropathy, and two exhibited subclinical polyneuropathy. Analysis of bulk samples of organic solvent used in the workplace revealed n-hexane concentrations of 10% to 65%. A statistically significant association was noted between n-
hexane concentration in the bulk samples and the prevalence of polyneuropathy.

Concentrations of n-hexane in the press-proofing factories exceeded 50 ppm (TLV). The airborne concentration of n-hexane in the main factory in which all six workers developed polyneuropathy was 190 ppm (26, 39). Additionally, victims who frequently worked overtime or slept in the factory had a high incidence of marked polyneuropathy, both clinically and electrophysiologically. The data indicated that high concentrations of n-hexane in the bulk samples and the habit of sleeping in the factories between shifts are risk factors for n-hexane polyneuropathy (26).

Although the first outbreak of n-hexane polyneuropathy occurred in 1983, and steps have been taken to reduce the content of n-hexane in organic solvents, the hazards of n-hexane poisoning were not well recognized by workers or even physicians. Measures to prevent excessive exposure at the worksites were not universally implemented. The second outbreak of n-hexane intoxication occurred in a ball-manufacturing factory in 1986 (27). The seven female victims developed polyneuropathy while processing of nylon fiber winding and cement coatings in a poorly ventilated room. Because the factory air was polluted by dust, the seven female workers attempted to enclose the fiber winding room. Therefore, although the room was free of dust, the air in the room accumulated high levels of n-hexane. The n-hexane concentrations in the personal air samples in the cement coating room ranged from 86 to 109 ppm, although the content of n-hexane in the bulk sample was low (14.1%) (27). The data indicate that a good ventilation system is far more important for preventing n-hexane polyneuropathy than n-hexane concentration in the bulk samples.

**CLINICAL MANIFESTATIONS**

**Peripheral nervous system (PNS) effects**

The clinical manifestation of n-hexane polyneuropathy is known as central-peripheral distal axonopathy or “dying-back neuropathy” (40). The onset is usually subacute or chronic, and the course is progressive with initial symptoms of numbness and burning sensation in the toes and fingers, followed by distal limb muscle weakness (26, 27, 39-41). The symptoms of polyneuropathy are usually symmetrical (42). Sensory impairments include reduced sensation of temperature, pin-prick, light touch, and vibration as well as position senses in the distal limbs (26, 41, 45). The muscle wasting usually occurs in the intrinsic hand and foot muscles, and muscle weakness often involves the extensor and flexor muscles of the legs and forearms. The extensor muscles are usually affected more severely than the flexor muscles in the forearms and legs (32, 45-46).

In severely intoxicated patients, proximal muscles may become weak with Gower’s phenomenon. Tendon reflexes are usually absent in ankle jerks and decreased in knee jerks and biceps (32, 45). Autonomic dysfunctions in glue sniffers often include nausea, vomiting, abdominal pain, impotence and skin changes such as coldness, sweating, and exfoliation (18). Cranial neuropathy includes blurred vision, impaired color vision, retinal or macular changes, decreased corneal reflexes and facial numbness (18, 43).

**Central nervous system (CNS) effects**

The neurotoxic effects of CNS after intoxication by n-hexane, MnBK, or 2,5-HD include headache, sleep disturbance, irritability, mental impairments and spastic gait (1, 7, 8). Acute exposure to high n-hexane concentrations may induce narcosis, euphoria, hallucination, dizziness, giddiness, and headache (7, 8). Severely intoxicated patients may develop respiratory depression, convulsion, coma, and even death. The acute effects are more common in glue sniffers than in industrial workers (1, 7).

Hyperreflexia with spasticity is usually observed in polyneuropathic patients several months after recovery of the peripheral neuropathy (7, 8). The sequelae of spasticity may persist for several years, even after cessation of n-hexane exposure. Extrapyramidal symptoms including rigidity, bradykinesia and tremor are not found. There are no cerebellar signs of nystagmus, tremor, ataxia, nor sphincter disturbance.

**CLINICAL COURSE AND PROGNOSIS**

Recovery from n-hexane polyneuropathy is slow and
usually begins after a period of deterioration known as “coasting”. Deterioration of muscle strength and sensory deficit is common and become maximal within 2-3 months after terminating exposure. The symptoms usually worsen for 2-5 months then slowly recover for 1-2 years. Except for severely intoxicated patients, the prognosis of n-hexane intoxication is usually favorable. Many patients recover within 1-3 years. In severely intoxicated cases, drop foot, claw hand and spastic gait may persist. Affected victims with sequelae are more likely to exhibit initial worsening.

ELECTROPHYSIOLOGICAL STUDIES

Electrophysiological studies of n-hexane polyneuropathy indicate primary axonal degeneration and focal demyelination. Characteristic changes are marked slowing of nerve conduction velocity (NCV) (decrease >40%), focal conduction block (reduction >50%) with temporal dispersion of compound muscle action potentials, and marked prolongation of distal latencies (>50%), particularly in the lower extremities. Sensory fiber involvement precedes that of the motor fibers. Electromyogram (EMG) changes of the distal lower limbs may occur earlier than those of the proximal limbs. Spontaneous activities with fast firing, high-amplitude polyphasic motor unit potentials are common. Long-term studies indicate that motor nerve function may improve, but the sensory nerves are more seriously affected and occasionally do not completely recover for as long as 10 years after exposure. The findings of series NCV studies also reveal initial worsening followed by slow recovery in the distal limbs. In the central nervous system, the slowing is much more pronounced than that in the proximal limbs, which indicates a distal axonopathy.

Studies of somatosensory evoked potentials studies show prolonged central conduction times. Brainstem auditory evoked potentials (BAEP) reveal prolongation of interpeak latencies of I-V as well. The data indicate that the spinal cord and the brainstem are also affected by chronic n-hexane intoxication. The absolute and interpeak latencies of the pattern-reversal visual evoked potentials (pVEP) are also prolonged. Furthermore, central conduction times calculated by transcranial magnetic stimulation and spinal nerve root stimulation indicate that the descending motor pathway is affected.

NEUROPATHOLOGICAL STUDIES

Sural nerve pathology

Biopsied sural nerve samples from the patients with n-hexane, MnBK, or 2,5-HD induced polyneuropathy show degeneration of both axon and myelin. Subperineurial edema and fusiform axonal enlargement with myelin retraction in the Ranvier nodes can be demonstrated by teased fiber preparation. Semithin sections may disclose huge axons of 25-35 u in diameter. Electronmicroscopic studies reveal a reduction of fiber density in the myelinated fibers and an increase in the collagen fibers in the endoneurium and perineurium. Axonal degeneration with mitochondrial clustering and neurotubule derangement also occurs. Histogram of myelinated fibers discloses marked reduction of large myelinated fibers with a relative preservation of small myelinated fibers. Giant axonal swelling is due to an accumulation of 10 nm neurofilaments and develops on the proximal sides of the Ranvier nodes.

Experimental studies

Exposure to n-hexane or its related neurotoxic substances causes distally accentuated axonal degeneration in the peripheral nerves as well as the central nervous system in experimental animals. In the PNS, characteristic giant axonal swelling, myelin thinning and axonal degeneration develop 4 days after 45 min. exposure of sciatic nerves to 2,5-HD. Electrophysiological abnormalities may precede the histopathological damage. In the CNS, the sites most vulnerable to these neurotoxic substances are the rostral regions of the long ascending tracts, dorsal spinocerebellar tracts, gracile, and cuneate regions, mamillary body, the lateral geniculate nucleus, and the superior colliculus. Dose-rate may determine the onset and progression of the neurotoxicity. The relative neurotoxic potency of n-hexane, MnBK, 2,5-HD and other metabolites have been examined. The time to achieve severe hindlimb weakness decreases from n-
hexane, 2-hexanol, MnBK, 2,5-hexanediol and 2,5-HD. Additionally, the eyes are also vulnerable to n-hexane exposure. Maculopathy and color discrimination defects are common.

PATHOGENESIS OF N-HEXANE POLYNEUROPATHY

n-Hexane is metabolized by hepatic cytochrome P450 to a series of metabolites, including the so-called γ-diketone such as 2,5-heptanediol, 6,6-octanediol, and 2,5-HD. Most metabolites are excreted in urine. The γ-diketone can react with ε-amine residues to form 2,5-dimethyl pyrroles, and covalent cross-linking of neurofilament protein. Only γ-diketones have neurotoxic effects while α, β and δ-diketones have none. Increasing evidence indicates that administration of 3,4-dimethyl substitution of 2,5-HD (3,4-DMHD) can accelerate pyrrole formation and impair axonal neurofilament transport. The neurotoxic effects of 3,4-DMHD can shift giant axon swelling from distal to proximal internodes. Therefore, 3,4-DMHD intoxication is assumed to link between the proximal 3,3′-iminodipropionitrile (IDPN) intoxication and those of the distal neurofilament axonopathies.

Animal studies have documented a relationship between slowing of fast axonal transport and focal axonal swelling. Axonal enzymes are conveyed from the perikaryon to the distal axon. Intoxication of IDPN is known to induce similar giant axonal swellings caused by selective blocking of neurofilamentous proteins traveling by long slow transport. The IDPN intoxication impairs neurofilament transport along the length of the axon. The 2,5-HD intoxication may also impair enzyme activity along the length of the axon. Diminished energy supplies cause local neurofilament accumulation and nerve degeneration.

The mechanisms of the continued progression despite cessation of exposure of neurotoxic agents remain unclear. However, storage of n-hexane or its metabolites within organs such as the nerve sheath and the rate of subsequent conversion to toxic metabolite such as 2,5-HD are plausible explanations.

TREATMENT AND PREVENTION

Patients with n-hexane intoxication have no known antidotes. Prevention of further excessive exposure to the n-hexane is the first step to prevent neuropathy. Increased awareness of these neurotoxic substances by industrial workers and glue sniffers, substitution of safer solvents in industrial processes, and lowering of the 8h-TLV time- weighted average may be helpful. Although an initial worsening of distal weakness may develop for several months, most patients can be assured of an eventual recovery. Supportive measures including physical and occupational therapy, may also be helpful.

REFERENCES


10. American Conference of Governmental Industrial Hygienist. TLVs and BEIs: threshold limit values for chemical substance and physical agents biological exposure index. Cincinnati, Ohio, ACGIH, 2005.


64. Mendell JR, Sahenk Z, Saida K, et al. Alterations of fast axoplasmic transport in experimental methyl n-butyl ketone...