Organic Solvent Toxicity
Module (Lecture) 14

Presenter

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DISCLOSURE**:**

Capt Fajardo does not have any financial arrangements or affiliations with any corporate organizations, which might constitute a conflict of interest with regard to this continuing education activity.

Lecture 14 –objectives:

Describe the etiologies of Organic Solvent Toxicity.
Understand the clinical presentation of patients with Organic Solvent exposure.
Identify the various Solvent compounds.
Identify the causative process of Benzene Reactions.
Understand the clinical presentation of Methanol Toxicity

Required reading:

Methanol Toxicity- Case Studies in Environmental Medicine
Benzene Toxicity- Case Studies in Environmental Medicine
COMDTINST M-6000.1 Medical Manual (sections on Benzene and Solvents)

NOTE: The two aforementioned required readings are part of the series of environmental case studies presented by the Agency for Toxic Substances and Disease Registry (ATSDR). These case studies are provided as supplementary material but are considered essential in order for the reader to acquire a full comprehension of the topic at hand. Additional case studies can be obtained on line at www.atsdr.cdc.gov/HEC/CSEM/. The evaluations and post-tests included as part of the ATSDR case studies cannot be credited as part of this lecture series. However, the reader may obtain credit by accessing the material and submitting directly to the ATSDR. In order to obtain proper accreditation for this lecture the reader must successfully complete the post-test included at the end of this presentation (score 70% or better).

INTRODUCTION

The purpose of this lecture is to present a clear picture of the dangers associated with the handling of organic solvents. Chapter 12 of the Coast Guard's Medical Manual has two protocols written specifically on this matter: Solvents and Benzene. The latter was written as a separate protocol, though Benzene is considered a solvent, due to the exposure of Marine Safety personnel in the late 60's and early 70's while inspecting what is commonly known as the "benzene barges" in many of our inland waterways. Individuals exposed to Benzene during those inspections are still actively enrolled in the Coast Guard's Occupational Medical Surveillance and Evaluation Program (OMSEP). Coast Guard medical providers should be intimately familiar with these surveillance protocols.

ORGANIC SOLVENTS:

Organic solvents are a distinct group of substances characterized by their ability to dissolve oils, fats, plastics, rubber and resins. Solvents are divided into different categories according to their chemical composition. It is interesting to note that solvents derived from the distillation of coal tar during the later part of the 19th century. The chemical industry found numerous applications for these previously unknown aromatic solvents as the science of organic chemistry emerged. Soon other raw materials, such as petroleum, replaced coal tar in the production of these solvents. As a result, products such as aliphatic hydrocarbons, different petroleum distillates and alcohols were introduced. Chlorine came into the market into the early 1920's as a byproduct of the alkali industry and was soon used to chlorinate aliphatic hydrocarbons leading to the introduction of chlorinated solvents into the market place. The use and often abuse of these products was soon followed by reports of toxic effects on exposed workers. Following is a brief description of some of the various chemical-types of solvents:

Aliphatic Hydrocarbons-

These straight-chain hydrocarbons are derived from the break down of petroleum. They include methane, ethane, propane, butane, pentane, hexane, pentane and octane as well as ethylene, propylene, butadiene, and isoprene. Some are pharmacologically inert but others are simple asphyxians or weak anesthetics. They may also produce mild mucous membrane irritation and central nervous system depression.

Aromatic Hydrocarbons-

These type chemicals consist of one or more benzene rings. Among these are benzene, toluene, styrene, ethylbenzene, xylene and naphthalene. They are mucous membrane irritants known to cause pulmonary edema, pneumonitis and

respiratory hemorrhages. They may also cause CNS depression, narcosis, organ liver failure, and cancer.

Halogenated Hydrocarbons-

This category includes compounds such as methyl chloride, methylene chloride, ethyl chloride, chloroform, methyl chloroform, bromoform, carbon tetrachloride, vinyl chloride and various other compounds. Their effects include renal and hepatic damage, cardiac sensitization, and carcinogenesis. Chlorinated hydrocarbons, which are the offending agents, associated with the effects of glue sniffing, have been known to cause cardiac arrhythmias. Other halogenated hydrocarbons include chlorobenzene, dichlorobenzene, and dieldrin, which have been reported to also cause renal and hepatic damage.

Esters-

Esters include acetate, ethyl silicate, ethyl formate, and methyl formate. They are comprised of phosphate, aliphatic and halogenated compounds. The aliphatic esters have an anesthetic effect in addition to causing irritation. The halogenated variety, on the other hand, tends to cause lacrimation, vesication and lung irritation while phosphate esters may cause central nervous system damage and neuropathy through cumulative effects.

Ketones-

Ketones are chemically stable substances, which include acetone, methyl ethyl ketone, methyl isobutyl ketone, and diisobutyl ketone. Exposure to high concentration of these agents can produce narcosis, headaches, nausea, vomiting, dizziness, loss of coordination, and loss of consciousness. At lower doses they can induce irritation of the eyes and respiratory passages and slow central nervous system activity. Respiratory failure and death have been reported with exposure to these agents.

Ethers-

Ethers are well known anesthetic agents with the propensity to cause irritation of the mucous membranes with possible resultant pulmonary edema, vomiting, headaches and nausea. They have carcinogenic properties and are also known as potent alkylating agents. This group includes methyl ether, isopropyl ether, chloromethyl ether, and chloromethyl methyl ether.

Alcohols-

Alcohols are hydrocarbons in which hydroxyl groups are substituted for one or more hydrogen atoms. Among these are methanol, ethanol, propanol, isopropanol, isobutanol, amyl alcohols, and allyl alcohols. Alcohol toxicity

increases progressively from ethyl to amyl to allyl alcohols and decreases as the higher alcohols become less soluble in body fluids. Alcohols are used as paint thinners and solvents. They generally cause irritation of the respiratory tract, tremors, headaches, pulmonary edema, diarrhea, convulsions, and vomiting as well as renal and hepatic damage.

Aromatic alcohols, also known as phenols, are very cytotoxic as a result of their ability to denature and precipitate proteins. They are strongly corrosive and induce a depressant effect on central nervous system function. Among these are phenol and cresol, which are readily absorbed through any exposure route. Others include dihydroxy (resorcinol), trihydroxy and chlorinated phenols.

Aldehydes-

Aldehydes are one of the most important types of industrial agents, which include acrolein, acetaldehyde, formaldehyde, furfural, and chloral hydrate. They are generally toxic though not carcinogenic and tend to cause marked edema, bronchitis, bronchopneumonia, asthma and pulmonary sensitization as a result of their strong mucous membrane irritation.

Amines-

These chemicals are among the most toxic solvents known. They are toxic to all tissues and are readily absorbed through all exposure routes. This group of chemicals includes methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, propylamine, butylamine, allylamine and cyclohexylamine. They produce methemoglobin are strongly irritant and act as corrosives.

Health Effects:

The health effect of these agents is dependant to a large extent on the route of exposure, the chronicity of exposure and the severity of the exposure. The differentiation between short-term and long-term exposures is like distinguishing between hours to days and months to years. This is important in helping to differentiate between the acute, subchronic and chronic effects of solvent exposure. *Acute effects* tend to resolve soon after discontinuation of the exposure; *subchronic effects* are most often reversible within 6 months and always within one year after discontinuation of the exposure; while *chronic effects* may not be reversible or only partially so within more than one year of termination of the exposure.

It should be noted that much of the knowledge on the effects of solvents is based on studies conducted in underdeveloped countries. Comments made about the safety level of these agents and the overall morbidity resulting from exposure to these agents may be influenced by the presence of other diseases, malnutrition and overall general health of the worker population in those countries.

Clinical Manifestations:

The toxicological effects common to most solvents are associated with their irritant effects on the mucous membranes, the effect on the skin and the depression of central nervous system function.

Irritant Effects-

Solvents vary in their potential for irritability of mucous membranes. Interaction between the solvent and the lipid layer of the cell membrane is thought to mediate this reaction. Although irritant effects seem to occur with most solvents, they appear to occur at levels considerably below current hygienic standards. In most cases the irritability disappears within a short period of time as a result of adaptation to the effects of the solvent. Most solvents irritate the mucous membranes of the eyes, nose and throat with the eyes being the most sensitive. The initial manifestation is typically a burning sensation, resulting from stimulation of the trigeminal nerve endings of the nose and eyes, although a cough may also be apparent as a result of stimulation of the laryngeal nerve endings in the throat. Aspiration of solvents into the lung can result in rapid and severe pulmonary damage. Heavy exposures are commonly manifested by cough, chest tightness and loss of breath. Strong irritant solvents such as toluene diisocyanate, acrolein and formaldehyde can induce symptoms at low exposure levels, while at high concentrations even common solvents like toluene, xylene and methylene chloride can induce pulmonary edema or chemical pneumonitis. The clinician should take note that due to surface tension and the low viscosity of organic solvents vomiting may lead to aspiration of solvents. As a matter of caution, vomiting should not be induced in the management of solvent ingestion.

Skin Effects-

Organic solvents account for approximately 20% of occupationally induced dermatitis with this condition being most commonly localized to the hands. The hands are commonly affected while cleaning with solvents, by accidents, or by not using proper protective equipment. The main effect of solvents results from the dissolving of fats from the skin, which with repeated exposures will result in a red, dry, itchy skin. Consequently, as a result of the difatting action the permeability of the skin to other toxic substances is increased thus enhancing the potential for skin absorption. Repeated exposures can lead to the development of an irritant contact dermatitis, a condition that accounts for 90% of the reported occupational shin diseases. Prolonged exposure and absorption may even cause a chemical burn.

This is illustrated by the effect of trichloroethylene on the skin. Although not a strong irritant, this product may cause a chemical burn through prolonged exposure or occlusion that occurs when cleaned clothes have not been properly dried. In the U.S. tetrachloroethylene is the main solvent used in dry cleaning. Exposure to this agent and other halogenated solvents may cause erythema,

blistering, burns or exfoliation. As a general rule, aromatic solvents tend to be more potent irritants than aliphatic solvents; alcohols are less irritating than aldehydes or ketones; esters are more potent irritants than alcohols; and carbon disulfide is one of the most irritating solvents.

Central Nervous System Effects-

The first neurological effects of solvent exposure were reported in the middle of the 19th Century with the use of carbon disulfide as the solvent for the vulcanization of rubber. A French physician August-Louis Delpech identified this solvent as the causative agent for the severe neuropsychiatric effects noted among rubber workers. Symptoms varied from fluctuations in mood, insomnia and memory problems to loss of sensations from different parts of the body and impotence. Inhalation of organic solvents may cause a progression of symptoms from an initial euphoria to lethargy, dizziness, staggering gait, coma and death-not unlike symptoms associated with alcohol intake. It is the initial euphoric "high" that has led to the abuse of solvents among youth groups, from glue sniffling and huffing, to become a widespread problem. Repeated and prolonged exposure to solvents may lead to permanent brain damage. Subtle changes in higher brain functions may manifest as sleep disturbances, anxiety, short-term memory loss, and behavioral changes. Symptoms described in case reports and cross-sectional studies of solvent-exposed workers include memory loss, problems with concentration, affective changes, fatigue, vertigo, decreased libido, sleep disturbances and vegetative symptoms.
Short-term exposure to organic solvents produces narcotic effects-headaches, dizziness, confusion-that are reversible after the termination of the exposure. Prolonged exposure, however, is associated with long-lasting central nervous system symptoms. Most workers are exposed to mixtures of aromatic and aliphatic solvents, such as that found in paints and lacquers, which include naphtha or xylene and toluene as the main components of the mixture. Painters, including those in the manufacturing industry as well as house and car painters, comprise one of the most important occupational groups with respect to solvent exposures. The time and appearance of symptoms appear to be related to previous exposure levels and at least a few years of exposure even among heavily exposed workers. Neuropsychological impairment progresses as long as the exposure continues.

Exposure Evaluation-

Solvent exposure may occur in many occupations and may result from work with agents with a wide difference of chemical properties and effects. A thorough and comprehensive lifetime solvent exposure evaluation is necessary to adequately assess a worker with possible solvent induced manifestations. Specific work conditions, overtime, additional jobs, hobbies and past employments must all be considered. Exposure levels are dependent on the area of use, artificial ventilation, temperature, workload, use of respirators and the worker's respiratory

rate. Symptoms of long-term solvent exposure are commonly seen and may be associated or related to other physical or mental health conditions. Therefore, it is crucial to determine the time of occurrence of symptoms as they relate to solvent exposure. Excessive alcohol consumption, chronic depression, previous history of head trauma, encephalitis or meningitis, presenile and senile dementia, ischemic brain disease and brain tumors may also produce a clinical syndrome indistinguishable from that seen with chronic solvent exposure.

Management-

Identification and prevention of neurotoxic hazards is the most important step. Little success has been achieved in the treatment of chronic toxic encephalopathy. Patients, who participated on a 10-week long rehabilitation program, involving intellectual training and verbal memory exercises, demonstrated a significant improvement on neuropsychological testing at the end of the program. However, after 6 months although a continuing reduction of emotional symptoms was reported, cognitive and somatic symptoms had increased to the original levels. Biologic monitoring of common solvents or their metabolites in end-exhaled air, blood or urine is essential to determine the amount of solvent taken up by the body. Preventive measures, including worker removal from the worksite, may be implemented in time to prevent the chronic effects of solvent overexposure.

Specific Agents:

Benzene-

Aromatic hydrocarbon produced by the burning of natural products- coal and petroleum. It is found in gasoline and other fuels and is used in the manufacturing of plastics, detergents and pesticides. It is a known carcinogen. Short-term exposure to high levels causes drowsiness, dizziness, loss of consciousness and death. Preventing evaporation, splashes and spills controls exposure.

Toluene-

Used as a sniffing agent. Tremor, ataxia and memory impairment are the most common reported symptoms, but cardiac arrhythmias, decrease sense of smell, optic atrophy, hearing impairment, and peripheral neuropathy may also occur. Long-term exposure has been associated with neuropsychiatric symptoms.

Styrene-

Induces a mild sensory neuropathy, which manifests as increased pain and tingling in the limbs. These effects are reversible if exposure is terminated within

4 weeks of the onset of symptoms. Styrene is a suspected carcinogen, however, its main metabolite, styrene oxide, is an established carcinogen.

Methylene Chloride-

Exposed workers are subject to developing heart disease. It also causes several types of tumors in animals and is considered carcinogenic by the International Agency for Research on Cancer. Methylene chloride is metabolized to carbon monoxide.

Carbon Tetrachloride / Chloroform-

Both of these agents induce significant hepatotoxicity, including terminal liver and kidney necrosis. These solvents interact with other agents, such as barbiturates and alcohol, to potentiate their hepatotoxic effects.

Trichloroethylene-

Exposure to this solvent in the mechanical engineering industry has been associated with an increased prevalence of neuropsychiatric symptoms. A psycho-organic syndrome characterized by intellectual impairment, memory deficiencies and affective changes has also been reported. At high exposure levels it may also induce a trigeminal neuralgia with facial numbness and weakness of the masticatory muscles.

Tetrachloroethylene-

Primary solvent used in the dry cleaning industry in the U.S. It has been associated with tumors of the urinary tract. Women working in laundries and dry cleaning have an increase risk of primary hepatic cancer.

Methanol-

This agent may damage the retina and induce blindness after ingestion of large amounts. These effects are not reported with occupational exposure.

Proceed to Post-Test