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REVIEW ARTICLE

Hydrocarbon toxicity: A review

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Context. Clinical effects of hydrocarbon exposure have been reported since 1897. These substances are ubiquitous, and their exposures are common. The specific hydrocarbon and route of exposure will determine the clinical effect, and an understanding of this is helpful in the care of the hydrocarbon-exposed patient. *Objective*. To complete a comprehensive review of the literature on hydrocarbon toxicity and summarize the findings. *Methods*. Relevant literature was identified through searches of Medline (PubMed/OVID) and Cochrane Library databases (inclusive of years 1975–2013), as well as from multiple toxicology textbooks. Bibliographies of the identified articles were also reviewed. Search terms included combinations of the following: hydrocarbons, inhalants, encephalopathy, coma, cognitive deficits, inhalant abuse, huffing, sudden sniffing death, toluene, renal tubular acidosis, metabolic acidosis, arrhythmia, dermatitis, and aspiration pneumonitis. All pertinent clinical trials, observational studies, and case reports relevant to hydrocarbon exposure and published in English were reviewed. Chronic, occupational hydrocarbon toxicity was not included. *Results*. Exposure to hydrocarbons occurs through one of the following routes: inhalation, ingestion with or without aspiration, or dermal exposure. Inhalational abuse is associated with central nervous system depression, metabolic acidosis, and arrhythmia. The exact mechanism of the CNS depression is unknown, but experimental evidence suggests effects on NMDA, dopamine, and GABA receptors. Chronic toluene inhalation causes a non-anion gap metabolic acidosis associated with hypokalemia. Halogenated hydrocarbon abuse can cause a fatal malignant arrhythmia, termed "sudden sniffing death". Individuals who regularly abuse hydrocarbons are more likely to be polysubstance users, exhibit criminal or violent behavior, and develop memory and other cognitive deficits. Heavy, long-term use results in cerebellar dysfunction, encephalopathy, weakness, and dementia. Neuroimaging may demonstrate leukoencephalopathy in these cases. Acute exposures improve with cessation of exposure. Electrolyte and fluid replacement will improve metabolic acidosis. Arrhythmias are precipitated via catecholamine surge, and beta blockers are presumed protective. Aspiration of hydrocarbons causes a potentially fatal pneumonitis. Symptoms may include cough, wheezing respiratory distress, and hypoxia. Bilateral interstitial infiltrates may be delayed for several hours after the development of pneumonitis. Treatment consists of supportive care, supplemental oxygen, and may require intubation and admission to an intensive care unit in severe cases. Unfortunately, aspiration pneumonitis remains a leading cause of poisoning mortality in children. Dermal exposure can cause dermatitis, chemical burns, and defatting injury. Oral exposure can cause local irritation as well as vomiting, diarrhea, and abdominal pain. *Conclusion*. Acute hydrocarbon exposure can result in a wide array of pathology, such as encephalopathy, pneumonitis, arrhythmia, acidosis, and dermatitis. Intentional inhalational and accidental ingestion exposures with aspiration lead to the greatest morbidity and mortality.

Keywords Inhalant abuse; Delirium; Toluene; Sudden sniffing death; Aspiration pneumonitis

Context

Structures and nomenclature

Hydrocarbons are organic compounds, containing primarily hydrogen and carbon, which are categorized as aliphatic (straight-chain) and aromatic (cyclic). Halogenated hydrocarbons contain atoms of halogen elements, such as chloride or fluoride, and may be aliphatic or aromatic. The hydrocarbons that are abused for euphoric effects via the respiratory route of exposure (e.g., toluene) are called inhalants. Toxicity is related to the dose, as well as the chemical characteristics of volatility, lipid solubility, viscosity, and surface tension. Those with higher volatility are better absorbed after inhalation. Lipophilic hydrocarbons cross the blood–brain barrier more readily and cause central nervous system (CNS) effects more often. Hydrocarbons with low viscosity and low surface tension are most likely to result in aspiration.

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History

The first death reported in the medical literature from aspiration of a hydrocarbon appears to be of a child in 1897.[1] Chlorofluorocarbons (CFCs) were developed in the 1930s, and heavy use continued until the 1970s when it was recognized that they were depleting the ozone layer. Reports of human toxicity from inhalant abuse began in the 1950s and 1960s as use of hydrocarbons became more widespread. Freon® (halogenated hydrocarbons used as

refrigerants) was abused beginning in the 1950s and was implicated in deaths in the 1970s.[2] Glue and other products containing hydrocarbons were initially abused on the West Coast in the 1960s, but then spread to the rest of the country. Case reports of sudden sniffing death emerged from that decade.[3] Aliphatic hydrocarbons replaced CFCs for many uses, but were also recognized to have toxic effects.

Common mixtures

Hydrocarbons are often found in mixtures and used as solvents for other ingredients. With any hydrocarbon exposure, a concern for the possibility of contaminants such as camphor, pesticides, and metals should be entertained. Historically, leaded gasoline caused elevated lead concentrations in those who abused the fumes.[4] Methanol toxicity is commonly a complication of inhalation of carburetor cleaner and other similar mixtures. Several studies indicate that methanol concentrations can be significant,[5] and vision loss is also reported.[6]

Epidemiology of exposure routes

There are three main types of hydrocarbon exposures: (1) children with usually unintentional ingestion of household hydrocarbons, (2) workers with dermal or inhalational occupational exposures, and (3) adolescents and young adults with intentional inhalational abuse. Epidemiology of hydrocarbon exposure is difficult to assess, as many exposures are unrecognized and either asymptomatic or minimally symptomatic. The American Association of Poison Control Centers reported 34,178 cases of hydrocarbon exposures in 2012, with 3,462 of those patients presenting to a health care facility, and 20 reported deaths.[7] An analysis of single-substance hydrocarbon exposures from 1994 to 2003 revealed that those substances with the highest hazard factors were benzene, toluene/xylene, halogenated hydrocarbons, kerosene, and lamp oil.[8]

Techniques of inhalant use include sniffing, huffing, and bagging. Sniffing is direct inhalation from a container, either the original container or an alternative into which the hydrocarbon is poured. Huffing is performed by soaking a cloth in the substance and holding it over the nose and mouth. This allows for increased concentration of inhaled fumes. Bagging is the process of breathing the vapor directly from a plastic or paper bag, thereby maximizing the concentration of inhaled fumes.

Methods

Relevant literature was identified through searches of Medline (PubMed/OVID) and Cochrane Library databases (inclusive of years 1975–2013), as well as multiple toxicology textbooks. Bibliographies of identified articles were also reviewed. Search terms included combinations of the following: hydrocarbons, inhalants, encephalopathy, coma, cognitive deficits, inhalant abuse, huffing, sudden sniffing death, toluene, renal tubular acidosis, metabolic acidosis, arrhythmia, dermatitis, and aspiration pneumonitis. All pertinent clinical trials, observational studies, and case reports relevant to hydrocarbon exposure and published in English were reviewed. Data regarding mechanism for hydrocarbon inhalant CNS effects, diagnostic evaluation, and treatment were included in this review article.

Results

Mechanisms of action

Neurologic. Inhaled hydrocarbons are absorbed through the lungs and enter the bloodstream. They are transported into the central nervous system (CNS), where their effects are most pronounced due to the high lipid content of neurons.[9] The vast majority of hydrocarbon inhalants act as CNS depressants.[10] However, the exact mechanisms through which the inhalant forms of hydrocarbons exert their effects on the CNS are unknown.

There have been multiple animal studies that have attempted to elucidate the mechanisms responsible for the CNS effects. The most research has been done with toluene. A study on the effect of toluene on N-methyl-D-aspartate (NMDA) and non-NMDA receptors using Xenopus oocytes found that acute toluene exposure resulted in a swift, noncompetitive, and reversible inhibition of NMDA receptors.[11,12] In a follow-up study, benzene, ethylbenzene, propylbenzene, trichloroethane, and xylene produced the same effects.[13] A study of toluene's acute effects on NMDA receptors in rat hippocampal neurons found that toluene affected the NMDA-mediated currents in a dose-dependent manner. During acute exposure conditions, the NMDA receptor currents were decreased, but following chronic exposure conditions, the NMDA-mediated currents were enhanced and there was increased expression of NMDA receptor subunits.[14] These chronic effects are postulated to be the result of increased neuronal excitability.[12]

Animal studies have also evaluated the dopamine pathway as a mechanism for CNS hydrocarbon inhalant effects. Inhalants have been found to activate mesolimbic dopamine neurons within the rat ventral tegmental area.[12,15–17] This increases dopamine concentrations in the caudate nucleus and nucleus accumbens in rats.[17,18] As with other drugs of abuse, this may be a mechanism for any addictive properties of inhalants.[16,17,19] Furthermore, chronic exposure to toluene in rats caused persistent dopamine dysfunction within the basal ganglia.[20]

The GABA transmission pathway has been another area of interest. Bowen et al. and Beckstead et al. have examined acute exposure of toluene, trichloroethane, and trichloroethylene. These substances have all been found to increase GABA and glycine receptor function in oocytes.[12,21] Additionally, toluene, trichloroethane, and trichloroethylene worked at the GABA synapses of CA1 pyramidal neurons in rats to inhibit the pyramidal neuronal functions.[15,21] This effect decreased with chronic exposure, suggestive of the development of a tolerance to these inhaled substances.[12,14] Other studies have also shown rat hippocampal damage with

chronic toluene exposure.[12,22] Toluene has been shown to induce oxygen radicals that persist in the CNS for 24 hours after toluene administration. The hippocampus appeared to be particularly vulnerable to the effects, suggesting a mechanism for increased hippocampal injury.[23] This appears to be most pronounced in the developing brain, including adolescence.[24] Because the function of the hippocampus is associated with learning and memory, this would provide a rationale for memory and learning difficulties that are experienced by inhalant abusers.[15,25–27]

Inhaled hydrocarbons also exert effects of less clear clinical significance on multiple other neurotransmitter and receptor systems.[12,14,28] These include serotonin (5HT3) receptors, nicotinic acetylcholine receptors, glutamate receptors, and voltage-gated ion channels.[12,14,20,28–30] These data support the notion that inhaled hydrocarbons act on multiple neurotransmitter and receptor systems in specific parts of the brain. Their effects appear to be dose and substance dependent.[31] Overall motor excitation occurs at low doses while sedation, coma, and death can occur at higher doses.[12,19,31,32]

Some hydrocarbons exert their clinical effect by metabolism into neurotoxins. Methyl n-butyl ketone and n-hexane have a common metabolite, 2,5-hexanedione, which causes peripheral neuropathy via axonal injury.[33,34] Methylene chloride itself can cause mucous membrane and respiratory irritation, but it then undergoes hepatic metabolism with resulting formation of carbon monoxide, producing delayed carboxyhemoglobinemia.[35]

Pulmonary. Hydrocarbons with low viscosity and high volatility (such as gasoline, kerosene, spot removers, and mineral spirits) are easily aspirated. Hydrocarbons disrupt surfactant, decreasing pulmonary compliance. They additionally cause pulmonary injury, with resultant inflammation, edema and necrosis,[36] as well as causing a direct inflammatory response.[37] Desquamation of pneumocytes also causes alveolar edema. Fluid and proteins fill the alveolar and interstitial spaces, and hemorrhage is possible.[38,39] The subsequent hypoxia is from a combination of ventilation–perfusion mismatch, shunt formation, and bronchospasm.[36] Animal experiments have shown that gastrointestinal absorption of hydrocarbons alone does not result in pneumonitis, but direct pulmonary exposure does cause pulmonary damage.[40]

Cardiac. Hydrocarbons, especially halogenated hydrocarbons, can induce arrhythmia. Exposure causes an increased sensitivity of the myocardium to epinephrine, the combination often precipitating a non-perfusing rhythm. Halogenated hydrocarbons are most likely to cause cardiac sensitivity. Non-halogenated hydrocarbons also can produce arrhythmia, with the exception of non-halogenated aliphatic hydrocarbons.[41] In addition to arrhythmias, halogenated hydrocarbons have negative inotropic, dromotropic, and chronotropic effects on cardiac tissue.[42]

Numerous studies have tried to elucidate the mechanism of arrhythmia caused by exposure to hydrocarbons. Various effects have been suggested as contributing to the cardiac sensitization. Slowing of repolarization and slowing of conduction create an opportunity for reentrant arrhythmias.[43] Several cardiac channels have been shown to alter their function after exposure to various hydrocarbons. Zhou et al. showed that hydrocarbons inhibit calcium influx into the cell.[44] Hydrocarbons also interact at the potassium channels hERG and IKs, as well as sodium currents.[43,44] Himmel showed that inhibition of calcium and potassium channels by volatile anesthetics facilitate after-depolarizations. The enhanced automaticity and triggered activity (from the after-depolarizations) are arrhythmogenic.[43] Another suggested mechanism is that conduction through gap junctions are inhibited by the combination of hydrocarbons and epinephrine, through dephosphorylation of connexin-43.[45]

Although the electrical function of the heart can be altered with acute exposure to hydrocarbons, prolonged use can cause structural damage that may also impede normal function. Samples of cardiac muscle taken from inhalant abusers have shown interstitial edema, intramyocaridal hemorrhages, contraction band necrosis,[46] edema, swollen and ruptured myofibrils,[47] and myocarditis and interstitial fibrosis.[48]

Renal. Abuse of toluene often results in metabolic acidosis, hyperchloremia, and hypokalemia. Most often this non-anion gap acidosis is from distal renal tubular acidosis.[49] Initially, however, an anion gap acidosis may form from production of organic acids as toluene is metabolized.[50] Several hepatic p450 enzymes (CYP 1A1/2, 2B6, 2C8, 2E1)[51] convert toluene to benzoic acid, which conjugates with glycine to form hippuric acid.[52] The kidneys excrete hippuric acid with ammonium, sodium, or potassium. The excretion of ammonium is limited, therefore large losses of sodium and potassium occur.[53] In a study of turtle bladders (which resemble human renal epithelial cells), toluene exposure resulted in a decrease in the rate of proton excretion, which could explain the development of the acidosis.[54]

Abuse of toluene is also associated with the development of proximal tubule dysfunction. Increases in excretion of β2 microglobulin, microalbumin, and enzymes from the brush border of the tubular cells are indications of proximal tubular damage.[53] Al-Ghamdi showed that proximal tubular injury was associated with CYP2E1 activity and oxidative stress in cell cultures.[55]

Clinical presentation

Acute inhalation. NEUROLOGIC. The acute CNS presentation of hydrocarbons can vary according to the specific substance inhaled.[56] In general, the symptoms of intoxication progress through a series of stages depending on the amount of inhalation of a particular substance. Each stage can be prolonged by inhaling repeatedly. The first stage is often described as euphoria, followed by excitability, disinhibition, and impulsive behavior.[9,10,19,30,32,57,58] In 1 case series of 43 cases of accidental occupational exposure to chlorodifluoromethane (Freon-22 ®) over 10 minutes, the most common symptoms were neurological and included headache, dizziness, and nausea. The next most common neurological symptoms were

dysesthesia of the tongue, numbness of the legs, muscular weakness, tinnitus, and blurred vision.[59] The second stage is characterized by CNS depression, such as slurred speech, confusion, hallucinations, diplopia, tremors, ataxic gait, visual changes, and weakness. The last stages are marked by drowsiness progressing to obtundation with possible coma, seizures, and death.[9,10,19,30,32,57–59]

High-frequency users may experience different acute inhalation symptoms when compared with low-frequency users. In a study of 267 adolescent inhalant users, high-frequency users were more likely to experience depressed mood, aggressiveness, irritability, amnesia, slurred speech, and suicidal ideation in addition to the previously described first-stage symptoms when acutely intoxicated. The low-frequency users did not experience these mood changes when acutely intoxicated.[56] Similarly, a study of 162 inhalant users evaluated in a psychiatric emergency department found higher rates of aggressive behavior, especially self-harm. The authors suggested that this was most pronounced in the acute stage. They also had worse ratings for measures of abstraction, insight, judgment, and immediate recall when compared to control psychiatric patients and poly-drug users.[60]

Acute inhalation has also been associated with a higher risk of polysubstance abuse, driving a motor vehicle under the influence, unprotected sexual intercourse, suffering serious physical injury, suicide attempts, committing acts of violence, vandalism, and committing property crimes.[58,60–62] In a case series of six acute toluene abusers, a blood concentration of more than 10mg/L was consistent with signs of CNS depression and impaired ability to drive.[58]

Acute inhalant exposure is not thought to result in long-term deficits[10,26,59]; however, studies have shown that recreational and occupational exposure can lead to more memory, attention, learning, and judgment deficits in the short term when compared to controls.[19,63] Similarly, a long-term assessment of a group of women with an accidental 3-day exposure to toluene and n-hexane while working at a tennis ball factory showed that these women still had slowing of verbal reasoning, particularly semantic and syntactic reasoning, on computer testing three years later.[64]

Cardiac. Death in the setting of inhalant abuse may be from anoxia, arrhythmia, brady-asystolic arrest or respiratory depression. Because most deaths are un-witnessed, and findings on autopsy cannot generally distinguish between them, it is unknown what the most common cause of death is in this setting. It is thought to be arrhythmia in most cases.[65] Sudden cardiac death after inhalation of hydrocarbons generally occurs after a period of heavy exposure to high concentrations followed by physical exertion or extreme excitation.[41] Experimental data suggest that hydrocarbons sensitize the myocardium, which may be enough to cause arrhythmia, but is more likely to happen with a surge of epinephrine. This phenomenon, referred to as "sudden sniffing death", was initially recognized in the 1960s by Bass, who subsequently published a case series in 1970.[3] Sudden fatal arrhythmia has been demonstrated in dogs who were exposed to high levels of toluene even without an identifiable catecholamine surge.[66]

Patients have presented with myocardial infarction thought to be from coronary artery vasospasm after abusing inhalants.[67] Cardiomyopathy has been reported after inhalant abuse also.[48]

Chronic inhalation. Neurologic. There is no definite timeframe in which inhalant abusers begin to display signs of chronic inhalation. Most of the signs do not develop until exposure frequency is 2–3 times per week for 6 months.[32] There are also no clear cumulative dose–response relationships.[25,68] The most frequent consequences are muscle weakness, tremor, peripheral neuropathy, cerebellar dysfunction, chronic encephalopathy, mood changes, loss of coordination, gait disturbance, spasticity, and dementia.[10,30,69–71]

Chronic hydrocarbon exposure results in various neuropsychological sequelae. The most frequent findings have been impairments in memory, attention, and learning.[19,25,26,63,64,68–72] One study assessed 15 painters over 14 months, with organic solvent exposure ranging from weeks to years. The most frequent symptoms were memory and learning deficits, impaired neuropsychological functioning, and personality changes.[73] A meta-analysis was performed in 2008 by Meyer-Baron et al. and found 46 studies with organic solvent exposure ranging from 3 to 31 years. The most consistent findings were deficits in multiple areas of attention, processing speed, short-term memory, and visual-spatial conceptualization.[25] Similarly, a systematic review of 30 studies involving chronic toluene abusers found that verbal measures of IQ were more affected than performance measures and deficits were most common in speed of processing, coordination, attention, learning, memory, executive abilities, insight, and judgment.[26] Surprisingly, adult users appear to have more severe deficits than chronic adolescent inhalant users.[74] Some studies have observed improvement after discontinuation, while others have noted static effects.[26]

Inhalant use at any age is highly associated with psychiatric disorders. Adult inhalant users had a prevalence of 48%, 36%, and 45% for development of a mood disorder, anxiety disorder, or personality disorder, respectively. The average age of inhalant users was younger than the average age of mood and anxiety disorder development, with the exception of social and specific phobias. This suggests that inhalant use may contribute to the development of these psychiatric disorders.[75] An additional disorder, amotivation syndrome, has also been described in association with inhalant use and is characterized by apathy, loss of initiative, disinhibition, and impulsiveness.[76] Any inhalant use in adults was associated with a 96% risk for at least one lifetime substance use disorder.[77] Adolescents are particularly susceptible to additional substance use. Adolescent inhalant users were more likely to acknowledge injection drug use. In all cases, a younger onset of inhalant use was associated with a higher rate of co-morbid conditions.[75,77,78]

Abnormal findings on neurological exams have been found in chronic petrol abusers, including postural tremor, positive palmomental reflex, dysdiadochokinesia, brisk deep tendon reflexes, abnormal tandem gait, and dysmetria, although it is unclear to what degree these symptoms were caused by lead toxicity. A positive palmomental reflex and abnormal tandem gait also persisted 6 months following discontinuation.[69] Chronic toluene abuse shares similar findings of ataxia, dysarthria, nystagmus, brisk deep tendon reflexes, postural tremor, and spasticity.[70]

A severe presentation of chronic inhalation is an induced encephalopathy.[57,71,79] Toluene and leaded petrol are the two most frequent hydrocarbons associated with this presentation. Leaded petrol abuse appears as a lead encephalopathy, including tremor, gross ataxia, eye movement abnormalities, and/or seizures.[14,30,71] Likewise, toluene encephalopathy is described by cognitive dysfunction (especially prefrontal), cerebellar dysfunction, spasticity, dementia, seizures, coma, and/or radiographic changes, termed leukoencephalopathy.[9,57,71,79] The most common neuropsychological impairments in solvent-induced encephalopathy are in attention, memory, learning, and fine-motor measures.[71,79]

Neuropathological changes of four solvent-induced leukoencephalopathy cases included severe and diffuse loss of myelin, mild loss of axons, and a reduction in numbers of oligodendroglia. Gliosis was also noted with a unique feature of PAS-positive macrophages in the absence of foamy macrophages.[79]

There is conflicting evidence regarding whether or not the consequences of chronic inhalation are reversible.[20,80] Most papers show a significant improvement with abstinence, but not always complete resolution.[20,26,57,72,80,81] Younger age, lower level of exposure, and better initial neurocognitive performance are predictive of an improved recovery.[68] Patients presenting with an encephalopathy have the worst rates of recovery.[26,57,68,80,81]

There are a few hydrocarbons that have been associated with specific neurological findings. Peripheral neuropathy is seen in chronic n-hexane[33,34] and methyl n-butyl ketone[82] exposure. Trichloroethylene is associated with cranial neuropathies, particularly trigeminal sensory involvement.[83] There is speculation that the trigeminal neuralgia may be due to reactivation of latent herpes simplex virus.[84] Ethylbenzene is associated with hearing loss.[85]

Renal. One common presentation for patients who abuse toluene is of muscle weakness due to severe hypokalemia. This can range from mild generalized lack of strength to flaccid paralysis.[86–88] It appears to spare the respiratory musculature.[89] Rarely, it can present as a focal weakness.[90,91] Some patients have gastrointestinal symptoms such as nausea, vomiting or diffuse abdominal pain in addition to the neurologic complaints.[91]

Patients can present with complaints of pyuria or hematuria.[53] Chronic metabolic acidosis may lead to calcium release from bone, and the subsequent development of kidney stones.[92] There are isolated reports of kidney disease from the development of autoantibodies against the glomerular basement membrane, with development of glomerulonephritis.[93]

Ingestion/Aspiration. Pulmonary injury from hydrocarbons most often occurs when young children ingest the liquid and aspirate during or after that event.[94] Alternative means of acquiring pulmonary injury include siphoning,[95] intravenous injection,[96,97] or "fire breathing" (a performance art in which liquid hydrocarbon is sprayed from the mouth over a flame[98]). In a retrospective chart review by Jolliff et al., the hydrocarbons most often associated with significant pulmonary injury were lamp oil, kerosene, and lighter fluid/naphtha.[94] Although pulmonary injury can occur without a history of vomiting, vomiting seems to be a risk factor for aspiration.[99]

Symptoms commonly reported after hydrocarbon aspiration are cough, nausea/vomiting, drowsiness, fever, tachypnea, tachycardia, and altered mentation.[39,100,101] Restlessness, stupor, agitation, and seizures are also reported.[101,102] Breath sounds can either be normal, or have rhonchi, wheezing, or rales.[39,102,103]

Exogenous lipoid pneumonia is a more chronic indolent form of pulmonary disease, and occurs after aspiration of hydrocarbons with high viscosity/low volatility, such as mineral oil or petroleum jelly. The usual symptoms are dyspnea and cough. Systemic illness is rare.[103–105] The development of lipoid pneumonia generally occurs in those with abnormal swallowing mechanism, such as through debilitation, alterations of consciousness, or neurologic deficit.[105,106] It is also an occupational disease in workers exposed to sprays of lubricants or other hydrocarbons.[105]

Dermal/Gastrointestinal/Miscellaneous. Hydrocarbons act as defatting agents, dissolving lipids in the skin.[107–109] Dermal or mucosal exposure can result in mild inflammation or more serious chemical burns.[110,111] Skin permeability depends on the size, lipophilicity, and structure of the hydrocarbon. They are sensitizers and repeated exposure can result in allergic dermatitis.[112] Huffers have been reported to develop perioral eczema, known as "glue sniffer's rash".[113] Inhalant abuse has also been reported to cause angioedema and frostbite injury.[114–117]

Injection of hydrocarbons has been reported to cause skin necrosis, thrombophlebitis, compartment syndrome, necrotizing fasciitis, and abscess formation. Systemic toxicity has been seen, such as fever, leukocytosis, and systemic inflammatory response syndrome (SIRS).[107,118] Pulmonary toxicity has been reported after intravenous injection of hydrocarbons.[96]

Exposure of the mucous membranes to hydrocarbons can result in irritation or chemical burns. Symptoms can include vomiting, diarrhea, and abdominal pain.[89] The primary concern after vomiting ingested hydrocarbons is development of pneumonitis.[108] The discomfort and vomiting are usually transient and do not require more than supportive care.[119]

Several halogenated hydrocarbons are associated with hepatotoxicity.[108,120] This largely occurs during occupational

exposure, and generally not with inhalant abuse (although case reports do exist[92]).[119]

Laboratory/Radiographic testing

Acute inhalation. Inhalants are notoriously difficult to capture on laboratory testing. They are not detected on routine urine drug screens[10] and there is no test that can capture the group as a whole.[121] Specific inhalants can be detected on gas chromatography if the chromatography is performed within 10 hours of exposure.[9] A recent study in 2007 showed that greater than 3 grams of hippuric acid (the metabolite of toluene) per gram of creatinine in the urine suggests exposure to toluene.[121] The sensitivity and specificity were 98.1% and 100%, respectively, for this test. In the case of suspected methylene chloride exposure, (i.e., occupational paint stripping or delayed-onset encephalopathy), carboxyhemoglobin concentrations should be obtained.

The most important role of laboratory testing in acute inhalant abuse is to assess the effects of inhalants on other organ systems. Suggested testing includes complete blood count, oxygen saturation, serum electrolytes, liver function tests, creatinine, glucose, and urinalysis.[9,32]

EKG changes may include prolonged QT,[43] ST segment elevation,[66] bradycardia,[42] AV blockade,[44,88] atrial fibrillation,[122] PVCs, supraventricular tachycardia,[89] and ventricular fibrillation.[67] Mice exposed to toluene and glue vapor and then had induced asphyxia developed AV block and bradycardia.[123]

There are no definite radiographic changes seen on head CT or brain MRI following acute inhalant abuse unless there are complications such as hypoxia or trauma.

Chronic inhalant abuse. Blood chemistries generally reveal low bicarbonate, low potassium, with no anion gap.[86] The hypokalemia can be profound at less than 2 mmol/L.[89] Creatinine concentrations are not usually elevated.[53] Elevated creatinine phosphokinase concentrations with rhadomyolysis are occasionally seen.[52,89] Hematuria and pyuria have been reported.[86,89,91]

The mechanisms of pathological and radiographic changes associated with chronic hydrocarbon inhalation are unknown.[68] Magnetic resonance imaging (MRI) abnormalities have been suggested to be related to cumulative inhalant doses.[124] It is not definite that these findings are a consequence of chronic hydrocarbon abuse rather than the result of a pre-existing condition; however, the majority of studies support the notion that these findings are a consequence of the abuse.[26] The most common radiological findings in chronic hydrocarbon abusers are white matter changes and subcortical abnormalities in the thalamus, basal ganglia, pons, and cerebellum.[10,70,125] One theory to explain these findings is that they are the result of axonal damage and gliosis. This is supported by Duncan et al. who found that choline concentrations, an increase of which is a marker of demyelination, did not change on imaging of the white matter in rat brains.[126] This is in direct contrast to Rosenberg et al. who found that white matter pathologies in chronic toluene abusers were related to myelin toxicity because axonal integrity appeared to be preserved and gliosis was minimal.[127]

White matter abnormalities began after 4 weeks of toluene exposure in rats. These changes appeared to start in the periventricular area and then extended into the subcortical white matter.[26,124] Periventricular and centrum semiovale white matter changes were the most common locations for 19 out of 41 chronic solvent abusers with a mean duration of abuse 4.6 years. Lesions also occur in the cerebellar white matter, internal capsule, brainstem, and upper cervical spinal cord.[124] In a study that compared diffusion tensor imaging on adolescent long-term inhalant users with cannabis users and controls, inhalant users had more severe callosal abnormalities than cannabis users, and both inhalant and cannabis users had more severe white-matter abnormalities in the medial temporal and callosal pathways than control subjects.[128]

A study by Okada et al. found that hypoperfusion in the prefrontal cortices was demonstrated in 14 out of 16 chronic solvent abusers on single-photon emission computed tomography (SPECT) imaging. This was independent of any frontal lobe atrophy. These findings were more prevalent than white matter abnormalities in the same subjects, suggesting that perfusion abnormalities may be an earlier and more sensitive sign than white matter changes. Furthermore, neuropsychological evaluation correlated avolition and apathy with the amount of hypoperfusion present in the prefrontal cortices.[76]

Other radiological findings in chronic inhalant abuse have included cerebral and cerebellar atrophy, atrophic dilatation of the ventricles, widening of the cerebral/cerebellar sulci, hypointensity in the thalami, hypointense red nuclei and substantia nigra, and hyperintense dentate nuclei.[26,70,124,127] Perfusion abnormalities have also been demonstrated in bilateral temporal/parietal regions in chronic inhalant abusers.[76]

Aspiration. Chest radiographs after acute hydrocarbon aspiration typically demonstrate bilateral interstitial infiltrates, which are usually in the middle and lower lobes.[98,99,101] Air bronchograms,[39] pneumatocele,[98,129] and pleural effusions,[97,98] have been reported. Radiologic abnormalities can last for months.[39]

Exogenous lipoid pneumonia manifests with consolidations, effusions, atelectasis, and fibrosis, and more often affects the lower lobes.[103,104,106] Chronic inflammation can cause fibrosis.[103,105] On CT scan, fat attenuation, ground glass opacities, linear or nodular opacities and masses are seen.[106] Chronic toluene abuse can be associated with panacinar emphysema or Goodpasture's syndrome.[130]

Differential diagnosis

Inhalation/Encephalopathy. A detailed history is the key to the diagnosis. The odor of hydrocarbons may be evident from chemical-soaked clothing, the patient's breath after ingestion or inhalation, or chemical-containing vomitus. Product

identification, if possible, allows complete determination of ingredients. This, in addition to the timing and route of exposure and the presenting signs and symptoms, allows prediction of the potential clinical effects.

The differential diagnosis includes sleep disorders, major depression, anxiety disorders, substance abuse and the excessive use of CNS-affecting medications, as well as neurodegenerative disorders, neurovascular disorders, neoplasms, metabolic causes, toxic encephalopathy (alcohol, drugs of abuse, lead, mercury), and traumatic brain disorders.[71]

Aspiration. Acute hydrocarbon pneumonitis can be confused with infectious lung injury, asthma, or exposure to pulmonary irritants. The appearance of exogenous lipoid pneumonia on chest radiograph can resemble pneumonia, ARDS, granuloma or carcinoma.[103] Intra-alveolar oils can coalesce into nodules and masses, surrounded by fibrosis called paraffinomas.[105]

Metabolic acidosis/Hypokalemia Other causes of non-ion gap acidosis are gastrointestinal losses, autoimmune disorders, and ureteral diversion.[131] Other etiologies of renal tubular acidosis are idiopathic hypercalciuria, primary hyperparathyroidism, lithium, and autoimmune disorders.[132] Hypokalemia may be caused by thyrotoxicosis, primary aldosteronism, licorice toxicity, profound diarrhea, Fanconi syndrome, and diuretics.[52,133]

Management/Disposition

Agitated delirium/Seizures. Benzodiazepines are the standard management of agitation and seizures that may occur with inhalant abuse, but there have been no studies directly assessing this treatment strategy. Most hydrocarbons are not known to be directly pro-convulsant; however, there is some evidence that chronic inhalation can alter neuronal structures in the brain (including the hippocampus) leading to the possibility of epilepsy.[14,22,124] Chronic management of epilepsy resulting from chronic inhalant exposure requires further study, but benzodiazepines are the mainstay of therapy for acute seizures. In the case of methylene chloride exposure and suspected carboxyhemoglobinemia, treatment with 100% oxygen should be initiated (further discussion of the management of carbon monoxide poisoning is beyond the scope of this review).

Gastrointestinal decontamination. Induction of emesis or gastric lavage should be avoided because of the risk of causing aspiration of ingested hydrocarbons.[40,95] Activated charcoal (AC) does adsorb hydrocarbons, but is known to cause gagging and vomiting,[134] which may lead to aspiration. If systemic effects are a greater concern than aspiration of the hydrocarbon, the use of AC could be considered, otherwise the risk of aspiration is a contraindication for its use.[135] According to the American Academy of Clinical Toxicology and European Association of Poison Centres and Clinical Toxicologists Position Paper regarding single-dose activated charcoal, AC should be avoided in cases of ingestion of highly volatile, low-viscosity hydrocarbons such as kerosene or lamp oil to avoid increasing the risk of aspiration.[136]

Airway/Mechanical Ventilation/Pneumonitis. In a retrospective study performed in the United States in 1969–1979, children with ingestion/aspiration who remained asymptomatic for 6 hours, and had a normal initial chest radiograph did not develop pneumonitis. Children who had an abnormal chest radiograph on presentation did not develop pneumonitis if they remained asymptomatic after a 6-hour observation period, and did not need repeat chest radiographs. If children were symptomatic and had an abnormal chest radiograph, they required admission to the hospital because the outcomes were difficult to predict in the initial observation period. Symptomatic children with normal initial chest radiographs did well if they became asymptomatic during the 6-hour observation, and could be discharged from the hospital.[137] A prospective observational study of phone calls to a poison center also demonstrated that asymptomatic patients (or patients who quickly resolved their symptoms) could also be safely observed at home.[138] In a prospective observational study performed in Egypt, children who exhibited wheezing, tachypnea, or altered mentation within 2 hours of their exposure were likely to require treatment at a health care facility, whereas children who did not exhibit one of those symptoms were most likely safe to be observed from home. This study also noted that chest radiographs were not sensitive, nor predictive of outcome.[102]

No large-scale trials have been performed to determine the best means of treatment for hydrocarbon aspiration. Antibiotics and steroids are generally considered not to be of great utility early in the course of illness, and should only be used if clear indications arise after the initial phases.[39] Case reports have documented success using extracorporeal membrane oxygenation,[139] surfactant,[140,141] and high-frequency oscillatory ventilation,[142] and high-frequency percussive ventilation.[143] In a rat model of kerosene-induced lung injury, partial liquid ventilation was shown to be detrimental and increased mortality.[36] In a sheep model of kerosene-induced lung injury, surfactant increased survival significantly.[38]

Tachydysrhythmias. Beta blockers have been suggested as a means of preventing the arrhythmia induced by sudden catecholamine surges in the setting of sensitized myocardium. The use of epinephrine and other catecholamines should be avoided in the acutely intoxicated patient, as they can precipitate arrhythmia.[144]

Electrolyte abnormalities. The mainstay of treatment for hypokalemia and metabolic acidosis from inhalant abuse is abstinence from further exposure. Fluid and electrolyte disturbances should be corrected and the patient should be on a cardiac monitor because of the risk of arrhythmia.[144] Most of the time, the electrolyte disturbances and acidosis will resolve after supportive care and cessation of exposure.[54,91] Caution must be used when treating with bicarbonate, as this may precipitate an intracellular shift of potassium, further

exacerbating hypokalemia.[86] Hypocalcemia has also been reported during resuscitation, with the potential of development of seizure and tetany.[86,89,92]

Substance abuse. There is very little in the medical literature on treatment for hydrocarbon inhalant exposure/abuse. A Cochrane review in 2010 attempted to identify randomized-controlled trials and controlled clinical trials of treatment for inhalant dependence and abuse; however, no studies met the inclusion criteria.[145] The authors' conclusions referenced previous recommendations for psycho-education and motivational interviewing for treatment.[32,145] This mirrors previous recommendations of cognitive behavioral therapy, multisystem and family therapy, 12-step facilitation, and motivational enhancement techniques.[10] A 2012 systematic review of psychosocial therapy for volatile substance use failed to find clear evidence of therapeutic effectiveness. There was limited weak evidence for efficacy of family therapy, programs encouraging outside activities, and residential programs run by indigenous agencies.[146] Finally, in a recent controlled trial, volatile substance use was significantly decreased one year after brief cognitive behavioral therapy intervention in a small group of adolescents.[147]

Evidence for pharmacologic treatment of hydrocarbon abuse is limited to case reports and small case series. There have been reports of successful neuropsychological symptom treatment with risperidone and lamotrigine.[145] A larger study of 40 males with inhalant-induced psychotic disorder found a 50% reduction in symptoms with the use of both carbamazepine and haloperidol; however, the carbamazepine-treated group had fewer extra-pyramidal side effects.[148] Baclofen decreased nonspecific withdrawal symptoms in three chronic inhalant users.[149] Lastly, there is some evidence that vigabatrin decreased the time rats spent in a toluene chamber, providing preliminary intrigue that vigabatrin may decrease the addictive properties of inhalants.[150]

Conclusions

Acute hydrocarbon exposure can result in a wide array of pathology, such as encephalopathy, pneumonitis, arrhythmia, acidosis, and dermatitis. Clinical effects can be predicted by substance, route of exposure, and dose. Intentional inhalational and accidental ingestion exposures with aspiration lead to the greatest morbidity and mortality.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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