PHOSGENE

Amongst the World War I trenches, amid the calamitous Bhopal, India contamination, or an unfortunate conflagration, phosgene has played an intriguing toxicological role. Pioneering efforts of Sir Davy Humphry led to its chemical genesis in 1812. Though infrequently implemented in modern warfare, phosgene exposures can result from releases in industrial and residential settings, in addition to terrorist threat. Chemical manufacturing of isocyanates, polyurethane, assorted dyes, and various pharmaceutical agents provide the majority of workplace exposures. Estimates suggest approximately one metric ton of phosgene continues to be generated annually as a by-product of United States industry. Phosgene is created by the combustion of chlorinated hydrocarbons, (methylene chloride, trichloroethylene, plastics). Additionally, phosgene exposure may occur from the endogenous metabolism of assorted compounds, including carbon tetrachloride and chloroform.

The occupational standard for permissible exposure limits to phosgene is 0.1ppm, as set by OSHA. Phosgene smells like freshly mowed hay, but exposure may go unnoticed until pulmonary irritation materializes. The combination of exposure duration (soak-time), in addition to the delayed development of severe pulmonary symptoms, creates a challenging poisoning scenario for the clinician.

Chemistry

Phosgene (CAS 1076) is also referred to as carbonic dichloride, carbonyl chloride, carbon oxychloride, or chloroformyl chloride. Phosgene is not a naturally occurring product. Several patented methods for its synthesis exist, including preparations from the reaction of chlorine and carbon monoxide filtered through charcoal, carbon monoxide together with nitrosoyl chloride, and carbon tetrachloride along with oleum. Phosgene is a colorless, gaseous compound at room temperature. At temperatures below 0°C, phosgene is transformed into a colorless, fuming liquid. Several hydrophobic solvents readily dissolve this acidic, chlorinated compound. Poorly hydrophilic, the minute amount of phosgene that dissolves is quickly hydrolyzed forming hydrochloric acid and carbon dioxide.

Pathophysiology

Although mildly irritating, phosgene does not produce severe toxicity until after it is hydrolyzed to hydrochloric acid and carbon dioxide. Inhaled phosgene penetrates deep into the lower respiratory tract where mucous-secreting goblet cells are not present in great numbers. Contact with bronchial epithelial cells and endothelial pneumocytes results in acute necrosis. Injury to Type I alveolar cells results in an inflammatory reaction with the development of edema and increased permeability (leaky membranes).

Type II pneumocytes are also affected and lose their ability to synthesize surfactant. Disruption of the structure of the alveolar-capillary barrier becomes evident.

Secondary, delayed effects may ensue after phosgene’s acidic properties interact with hydroxyl, sulhydril, or amine groups of biological importance. Typical free-radical scavengers (i.e. glutathione) rapidly become exhausted and irreversible binding to key proteins ensues. Depletion of albumin, enzymes, and vitamins becomes apparent. Lipid peroxidation proceeds, endangering lung tissue stability and permeability. Free radical formation gradually diminishes via scavenger interaction or free radical interaction. Thirdly, an inflammatory response increases pulmonary insult. Oxygen radicals likely mediate primary and secondary injuries effects, producing proinflammatory agents. The combined production of lipoxygenase-derived leukotrienes and the formation of arachidonic acid can affect pulmonary architecture and membrane integrity, with increased cellular permeability.

Laboratory experimentation suggests phosgene does not induce pulmonary constriction via the formation of thrombosome synthesis. Additionally, neutrophils traverse the alveolar/capillary barrier promoting injury and edema. While the lungs are the primary target of phosgene-induced injury, severe intoxication may produce hemolysis, hepatic necrosis, and renal impairment. Severe cases precipitate acute respiratory distress and death.

Phosgene-oxime, a structurally similar compound, also produces significant toxicity. Phosgene-oxime is a known vesicant, resulting in immediate dermal necrosis. Inhalation or ocular exposure to phosgene-oxime can produce severe mucosal damage.

Symptomology

Initial phosgene symptoms are those typical of a respiratory irritant. Common symptoms include coughing, nausea, vomiting, headaches, lethargy, dizziness, and oral/throat irritation. The formation of acids is prolonged, causing irritation of the mucous membranes. Rarely, lacrimation and conjunctivitis are also evident on presentation, strongly indicating a severe exposure. Phosgene-related toxicity typically does not resolve following fresh air/ventilation as is often apparent with non-oxidant respiratory irritants. Although not diagnostic, failure of improvement of a patient’s symptoms after the contamination is removed, may signal the presence of phosgene or another strong oxidant.

Symptoms progress steadily, with persistent cough and dyspnea. The earlier these symptoms and signs of toxicity develop, the greater the toxic consequences. The appearance of a frothy sputum, deteriorating arterial blood gases, infiltrates on a chest radiograph, or the need for intubation and mechanical ventilation often signals the onset of pulmonary edema. The latency period from phosgene exposure to the development of pulmonary edema may range from two to upwards of forty-eight hours. As time progresses, severely intoxicated patients become hypovolemic and hypotensive, with respiratory distress rapidly progressing to a non-cardiac pulmonary edema. Morbidity after phosgene exposure tends to occur within the initial forty-eight hour post-exposure period.
Treatment

Despite the long experience with phosgene exposures, there have not been many therapeutic advances. The removal of the patient from the contaminated source remains optimal first aid for exposed patients. Rescuers should remove all contaminated clothing and flush the ocular and dermal regions with copious amount of water. Patients must be admitted to health care facilities for close observation and potential treatment. Phosgene's delayed toxicity suggests the need for a prolonged period of observation, often in an intensive care unit where ventilatory assistance can be employed. Continual monitoring of pulmonary function and oxygenation is recommended with frequent blood gases and chest x-rays as needed. Ventilation with high concentrations of inspired oxygen with positive end expiratory pressure is suggested. Vital signs should be noted frequently as a response to hypotension or a hypovolemic state may be warranted.

Patients with a severe intoxication should have evaluation of both liver and kidney function. Diuretics are not recommended, for phosgene toxicity is not a consequence of a hypovolemic crisis. Bronchodilators and prophylactic antibiotics have been effective in diminishing phosgene-induced pulmonary edema. Patients with pulmonary edema may require monitoring of pulmonary wedge pressures. Patients who develop pulmonary edema respond well to use of parenteral corticosteroids.

Patients exhibiting symptoms should be admitted overnight and followed thoroughly until all symptoms resolve. Generally, symptoms are likely to arise within the first twenty-four hours after exposure. If symptoms are not present during this duration, the patient may be discharged after adequate education of delayed and long-term symptoms are provided.

Several compounds have provided additional protection against phosgene-induced pulmonary edema in laboratory models. Ibuprofen, cyclophosphamide, and colchicine have positive effects on decreasing neutrophilic migration; significantly decreasing phosgene induced pulmonary edema in animal models. N-acetylcysteine, a GSH agonist, prevents pulmonary lipid peroxidation, though NAC as a specific phosgene antidote has not been evaluated. Several pharmaceutical agents responsible for increasing cAMP production have protective laboratory responses to phosgene toxicity, including: dibutyryl cAMP, aminophylline, and β-adrenergic agonists. Pentoxifylline appears to have no protective effect on pulmonary insult.

Hexamethyleneetramine (HMT) was originally believed to protect against phosgene toxicity and it was employed as an antidote during World War I. However, subsequent laboratory results have disproved any post exposure protection, though, pretreatment may minimize toxicity.

Mass contamination with phosgene may surface as a single agent or in occurrence with another terrorist agent; likely a pulmonary targeted agent. If a mass exposure is believed to have occurred, first responders should immediately contact the local poison control center and public health authorities.

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REFERENCES