Toxicity, Chlorine Gas

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Introduction

Background

Chlorine gas is a pulmonary irritant with intermediate water solubility that causes acute damage in the upper and lower respiratory tract. Chlorine gas was first used as a chemical weapon at Ypres, France, in 1915. Of the 70,552 American soldiers poisoned with various gases in World War I, 1843 were exposed to chlorine gas. \[1\]

Pathophysiology

Chlorine is a greenish-yellow, noncombustible gas at room temperature and atmospheric pressure. The intermediate water solubility of chlorine accounts for its effect on the upper airway and the lower respiratory tract. \[2\]

Exposure to chlorine gas may be prolonged because its moderate water solubility may not cause upper airway symptoms for several minutes. In addition, the density of the gas is greater than that of air, causing it to remain near ground level and increasing exposure time. The odor threshold for chlorine is approximately 0.3-0.5 parts per million (ppm); however, distinguishing toxic air levels from permissible air levels may be difficult until irritative symptoms are present.

Chlorine is moderately soluble in water and reacts in combination to form hypochlorous (HOCl) and hydrochloric (HCl) acids. Elemental chlorine and its derivatives, hydrochloric and hypochlorous acids, may cause biological injury. The chemical reactions of chlorine combining with water and the subsequent derivative reactions with HOCl and HCl are as follows:

a1) \( \text{Cl}_2 + \text{H}_2\text{O} \rightleftharpoons \text{HCl} \text{ (hydrochloric acid)} + \text{HOCl} \text{ (hypochlorous acid)} \text{ or} \)

a2) \( \text{Cl}_2 + \text{H}_2\text{O} \rightleftharpoons 2 \text{HCl} + [\text{O}^-] \) (nascent oxygen)

b) \( \text{HOCl} \rightleftharpoons \text{HCl} + [\text{O}^-] \)

Mechanism of activity

The mechanisms of the above biological activity are poorly understood and the predominant anatomic site of injury may vary, depending on the chemical species produced. Because of its intermediate water solubility and deeper penetration, elemental chlorine frequently causes acute damage throughout the respiratory tract. \[2\] Cellular injury is believed to result from the oxidation of functional groups in cell components, from reactions with tissue water to form hypochlorous and hydrochloric acid, and from the generation of free oxygen radicals. Although the idea that chlorine causes direct tissue damage by generating free oxygen radicals was once accepted, \[3\] this idea is now controversial. \[4,5\]

Solubility effects

Hydrochloric acid is highly soluble in water. The predominant targets of the acid are the epithelia of the ocular conjunctivae and upper respiratory mucus membranes. \[6\]

Hypochlorous acid is also highly water soluble with an injury pattern similar to hydrochloric acid. Hypochlorous acid may account for the toxicity of elemental chlorine and hydrochloric acid to the human body. \[7\]
Early response to chlorine gas

Chlorine gas, when mixed with ammonia, reacts to form chloramine gas. In the presence of water, chloramines decompose to ammonia and hypochlorous acid or hydrochloric acid. The early response to chlorine exposure depends on the (1) concentration of chlorine gas, (2) duration of exposure, (3) water content of the tissues exposed, and (4) individual susceptibility.

Immediate effects

The immediate effects of chlorine gas toxicity include acute inflammation of the conjunctivae, nose, pharynx, larynx, trachea, and bronchi. Irritation of the airway mucosa leads to local edema secondary to active arterial and capillary hyperemia. Plasma exudation results in filling the alveoli with edema fluid, resulting in pulmonary congestion.

Pathologic findings

Pathologic findings are nonspecific. They include severe pulmonary edema, pneumonia, hyaline membrane formation, multiple pulmonary thromboses, and ulcerative tracheobronchitis.

The hallmark of pulmonary injury associated with chlorine toxicity is pulmonary edema, manifested as hypoxia. Noncardiogenic pulmonary edema is thought to occur when there is a loss of pulmonary capillary integrity, and subsequent transudation of fluid into the alveolus is present. The onset can occur within minutes or hours, depending upon severity of exposure. Persistent hypoxemia is associated with a higher mortality rate.

The eye seldom is damaged severely by chlorine gas toxicity; however, burns and corneal abrasions have occurred. Acids formed by the chlorine gas reaction with the conjunctival mucous membranes are buffered, in part, by the tear film and the proteins present in tears. Consequently, acid burns to the eye typically cause epithelial and basement membrane damage but rarely damage deep endothelial cells. Acid burns to the periphery of the cornea and conjunctiva often heal uneventfully, while burns to the center of the cornea may lead to corneal ulcer formation and subsequent scarring.

In animal models of chlorine gas toxicity, immediate respiratory arrest occurs at 2000 ppm, with the lethal concentration for 50% of exposed animals in the range of 800-1000 ppm. Bronchial constriction occurs in the 200-ppm range with evidence of effects on ciliary activity at exposure levels as low as 18 ppm. With acute exposures of 50 ppm and subacute inhalation as low as 9 ppm, chemical pneumonitis and bronchiolitis obliterans have been noted. Mild focal irritation of the nose and trachea without lower respiratory effects occur at 2 ppm.

In one study of chlorine gas toxicity conducted on human volunteers, 4 hours of exposure to chlorine at 1 ppm produced significant decreases in forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and peak expiratory flow rate. An increase in airway resistance was demonstrated. In a controlled volunteer study, patients with hyperreactive airways demonstrated an exaggerated airway response to exposure of 1 ppm chlorine gas. While in another study, patients with rhinitis and advanced age demonstrated a significantly greater nasal mucosal congestive response to chlorine gas challenge than patients who did not have rhinitis or those of younger age. However, the mechanism of response to chlorine in nasal tissue does not appear to include mast cell degranulation.

Frequency

United States

Chlorine gas is one of the most common single, irritant, inhalation exposures, occupationally and environmentally. In 1983, an estimated 191,000 US workers were at risk of exposure to chlorine in various forms. In a recent study of 323 cases of inhalation exposures reported to poison control centers, the largest single source of exposure (21%) was caused by mixing bleach with other products. The greatest number of victims were injured in manufacturing and the entertainment and recreation services sectors.
International

Internationally, chlorine gas accounts for the largest single cause of major toxic release incidents.[16] Use of chlorine internationally is parallel to use by the US in chemical, paper, and textile industries and in sewage treatment.

Mortality/Morbidity

Five-year cumulative data (1988-1992) from the American Association of Poison Controls Centers’ National Data Collection System revealed 27,788 exposures to chlorine. Of these exposures, the outcome was categorized in 21,437 cases; 40 resulted in a major effect, 2091 resulted in a moderate effect, 17,024 resulted in a minor effect, and 2099 had no effect. Three fatalities occurred.[17,18,19,20,21] Another case series associated worse outcomes with advanced age, initial low peak expiratory flow rate (PEFR), exposure in an enclosed space, and prolonged short- and long-term exposure.

- Minor effects include signs or symptoms that are minimally bothersome and quickly resolved.
- Moderate effects include signs or symptoms that are more pronounced or more prolonged than minor effects. These may have a systemic nature and usually require some form of treatment.
- Major effects include signs or symptoms that are life-threatening or result in significant residual disability or disfigurement.

Clinical

History

- Cough (52-80%)
- Shortness of breath (20-51%)
- Chest pain (33%)
- Burning sensation in the throat and substernal area (14%)
- Nausea or vomiting (8%)
- Ocular and nasal irritation (4-6%)
- Choking
- Muscle weakness
- Dizziness
- Abdominal discomfort
- Headache

Physical

- Decreased breath sounds
- Tachypnea
- Tachycardia
- Wheezing
- Nasal flaring
- Intercostal and subcostal retractions
- Cyanosis
- Rhinorrhea
- Lacrimation
- Hoarseness of the voice or stridor
- Rales (acute respiratory distress syndrome [ARDS]/noncardiogenic pulmonary edema)
- Crepitus (associated with pneumomediastinum)[22]

Causes

- Chlorine gas is one of the most common single, irritant, inhalation exposures, occupationally and environmentally. Possible sources of exposure are as follows:
  - Industrial bleaching operations
  - Sewage treatment
  - Household accidents involving the inappropriate mixing of hypochlorite cleaning solutions with acidic agents
  - Transportation releases
  - Swimming pool chlorination tablet accidents[23]
  - Storage tank failure
  - Chemical warfare
- Adverse effects of inappropriate mixtures of household cleaners usually are caused by prolonged exposure to an irritant gas in a poorly ventilated area. The most common mixtures of cleaning agents are sodium hypochlorite (bleach) with acids or ammonia. Potential irritants released from such mixtures are chlorine gas, chloramines, and ammonia gas.

Differential Diagnoses

<table>
<thead>
<tr>
<th>Acute Respiratory Distress Syndrome</th>
<th>Toxicity, Ammonia</th>
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<td>Burns, Thermal</td>
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<td>Chronic Obstructive Pulmonary Disease and Emphysema</td>
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<tr>
<td>Pneumonia, Viral</td>
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Other Problems to Be Considered

- Sulfur dioxide toxicity
- Nitrogen dioxide toxicity
- Hydrogen fluoride toxicity
Metal fume fever

**Workup**

**Laboratory Studies**

- Arterial blood gas
  - Abnormalities include hypoxia and metabolic acidosis.
  - The metabolic acidosis may be hyperchloremic (nonanion gap). A postulated mechanism for the production of this acidosis is the absorption of hydrochloric acid following the reaction of chlorine gas with water.

**Imaging Studies**

- Chest x-ray (CXR) findings often are normal, but a CXR may be indicated to rule out pulmonary edema, pneumonitis, and acute ARDS.
- Ventilation perfusion scan
  - Abnormal retention of radiolabeled xenon gas at 90 seconds suggests lower airway injury.
  - Ventilation perfusion scans have been used to determine lung damage in smoke inhalation.

**Other Tests**

- Monitor oxygen saturation.
- Obtain an electrocardiogram (ECG).
- Pulmonary function tests may indicate obstructive or restrictive patterns.
- PEFRs may reveal obstructive airway disease and response to therapy.

**Procedures**

- Perform a fiberoptic laryngoscopy or bronchoscopy with intubation, as necessary, if laryngospasm is suspected or clinically evident.

**Treatment**

**Prehospital Care**

Prehospital care providers should take necessary precautions to prevent contamination. The use of a chemical cartridge respirator or self-contained breathing apparatus with full face mask should protect against the effects of chlorine gas. However, in the setting where other potential chemical exposures exist, higher levels of protection should be considered.

- Remove the individual from the toxic environment.
- Bring container, if applicable, so medical personnel can identify toxic agent.
- Commence primary decontamination of the eye and skin, if necessary.
- Real-time measurement of chlorine gas, both quantitative and qualitative, is possible through the use of...
mobile equipment.

Chlorine gas is denser than air and accumulates close to the ground. Therefore, during chlorine-related accidents, people should be instructed to seek higher altitudes to avoid excessive exposure.

For related information, see Medscape’s Disaster Preparedness and Aftermath Resource Center.

**Emergency Department Care**

- **Decontamination**
  - Eye and skin exposures require copious irrigation with saline. In cases of suspected ocular injury, determine initial pH using a reagent strip. Continue irrigation with 0.9% saline until the pH returns to 7.4.
  - Topical anesthetics help limit pain and improve patient cooperation.
  - Following irrigation, perform slit lamp examination, including fluorescein staining.
  - Measure ocular pressures.
  - Treat corneal abrasions with antibiotic ointment.

- **Supplemental oxygen**
  - Maintain a PaO$_2$ of 60 mm Hg or greater.$^{[27]}$
  - Long-term (>24 h) elevated fraction of inspired oxygen (FiO$_2$) greater than 50% may result in oxygen toxicity.

- **Fluid restriction in patients with ARDS**

- **Treatment of bronchospasm**
  - Bronchodilators (inhaled albuterol or other beta-agonists) have been used frequently for the management of respiratory symptoms. Animal models have demonstrated improvements in blood gas parameters, airway pressure, and lung compliance with the administration of aerosolized terbutaline.
  - The role of inhaled ipratropium is not well defined.
  - Lidocaine (1% solution) added to nebulized albuterol results in both analgesic and cough-suppressant actions.

- **Intubation for laryngospasm**
  - Fiberoptic aid may be required if significant edema is present.
  - Consider using the largest size endotracheal tube possible to optimize pulmonary toilet.

- **Hypoxemic respiratory failure**
  - Treat with positive-pressure ventilation.
  - High positive end-expiratory pressure (PEEP) (8-10 mm Hg) and inverse ratio ventilation may be beneficial in ARDS.
  - In an animal model, prone positioning immediately following exposure to chlorine gas improved pulmonary function, whereas treatment in the supine position was associated with further compromise of pulmonary gas exchange.

- **Sodium bicarbonate**
  - Use of nebulized solution of sodium bicarbonate, while recommended by some authors,$^{[28,29]}$ lacks sufficient clinical evidence.
  - The mechanism of action is thought to be through the neutralizing of the hydrochloric acid formed.
when chlorine gas comes into contact with water. Lack of clinical trials and the theoretical possibility that an exothermic reaction may be produced when bicarbonate mixes with hydrochloric acid have led some authors to question its use. Nonetheless, several pediatric and adult case reports did describe a clinical improvement in patients with chlorine gas induced pulmonary injury who are treated with inhaled sodium bicarbonate.

- In a randomized, controlled trial 44 patients received either nebulized sodium bicarbonate (4 mL of 4.20% NaHCO₃ solution) or saline treatment following chlorine gas exposure. Treatment of all patients included corticosteroids and nebulized, short-acting β2-agonists. Compared to the placebo group, the NaHCO₃ group had significantly higher FEV1 values at 120 and 240 min.

- Steroids
  - Parenteral steroids, while advocated by some authors to prevent short-term reactions and long-term sequelae, are not recommended by others because of insufficient clinical trials.
  - Animal studies suggest improvements in pulmonary function and lung compliance with treatment of inhaled steroids, alone and in conjunction with aerosolized beta-agonists. Earlier administration of inhaled steroids in animal studies was associated with more beneficial effects.

- Prophylactic antibiotics are not recommended.

Consultations

- Consult critical care personnel if patient exhibits severe and protracted respiratory distress.
- Consult an ophthalmologist for patient with ocular burns.
- Consult a medical toxicologist if one is available in the area.

Medication

Beta-agonists, although not well studied in humans, have been widely used for the management of respiratory symptoms in chlorine gas exposure, and they have demonstrated efficacy in animal models. They should be considered a first-line agent in the setting of chlorine gas exposure and respiratory symptoms or signs.

Bronchodilators

Bronchodilatation through respiratory smooth muscle relaxation improves the respiratory status of the person who is exposed to chlorine gas.

Albuterol (Proventil, Ventolin)

Beta-agonist for bronchospasm. Relaxes bronchial smooth muscle by action on beta2-receptors with little effect on cardiac muscle contractility.

Dosing

Adult

5 mg in 2.5 mL NS for nebulization prn

Pediatric

0.2 mg/kg/dose PO prn

Interactions

Beta-adrenergic blockers antagonize effects; inhaled ipratropium may increase duration of bronchodilatation by
albuterol; cardiovascular effects may increase with MAOIs, inhaled anesthetics, TCAs, and sympathomimetic agents

Contraindications
Documented hypersensitivity

Precautions

Pregnancy
C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions
Caution in hyperthyroidism, diabetes mellitus, and cardiovascular disorders; promotes tachycardia, especially in children; may cause or exacerbate tachydysrhythmias

Inhaled corticosteroids
Anti-inflammatory inhaled corticosteroids have been shown in animal models to improve respiratory function following experimental chlorine gas exposure. Exact mechanism of function in chlorine gas exposure unclear.

Budesonide (Pulmicort, Rhinocort)
Second-line agent for use in moderate-to-severe exposures.

Dosing

Adult
200-400 mcg, via oral inhalation, twice initially; may increase to 800 mcg bid

Pediatric
200 mcg, via oral inhalation, twice initially; may increase to 400 mcg bid

Interactions
None reported

Contraindications
Documented hypersensitivity

Precautions

Pregnancy
C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions
Prolonged use, application over large surface areas, application of potent steroids, and occlusive dressings may increase systemic absorption of corticosteroids and may cause Cushing syndrome, reversible HPA axis suppression, hyperglycemia, and glycosuria; adverse effects include oral thrush, hoarseness, adrenal suppression, glaucoma, skin bruising, and alteration in bone metabolism

Aerosolized sodium bicarbonate
When inhaled, these agents may neutralize (if administered early) or counteract the effects of inhaled chlorine.
Sodium bicarbonate (Neut)

Theoretical reason for use is to reduce tissue injury caused by the acidic agent in airway. May not be useful if patient does not present immediately postexposure. Route of administration is inhalation via nebulizer.

Dosing

**Adult**

4 mL of a 3.75% solution made by diluting 2 mL of a standard 7.5% solution with 2 mL NS inhaled via nebulizer; administer once; repeat prn

**Pediatric**

Administer as in adults

**Interactions**

Theoretical exothermic reaction by an interaction with acidic inhalant

**Contraindications**

Documented hypersensitivity

**Precautions**

**Pregnancy**

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

**Precautions**

Use not well established; monitor for complications while administering

**Follow-up**

**Further Inpatient Care**

- Consider hospitalization to observe and treat the patient with chlorine gas exposure in a highly monitored setting in any of the following cases:
  - Symptoms persist after 6 hours.
  - Patient was severely exposed.
  - Child was exposed.
  - Patient has a history of underlying respiratory or cardiovascular disease.

- Some authors suggest observation for a minimum of 24 hours because pulmonary edema may occur for 24 hours after exposure. Pulmonary edema occasionally may induce severe hypoxemia in minutes.

- Patients who are asymptomatic 24 hours after exposure may be discharged from hospital.[35]

- For a severe reaction, follow up with a pulmonologist.

**Further Outpatient Care**

- No hospitalization is required for mild chlorine exposure or for patients who remain asymptomatic.
Transfer

- Transfer, as necessary, if local resources (eg, critical care, toxicologist, pulmonologist) are not available.

Deterrence/Prevention

- Deterrence may decrease the number of accidental exposures to chlorine gas. Proper descriptions on swimming pool chlorinator solutions with detailed warnings to avoid mixing solutions would prevent a great number of accidents.
- As accidental occupational exposures to chlorine gas comprise a significant percentage of severe exposures, proper methods of training and supervision are beneficial. Proper enforcement of regulations covering these work situations should be helpful.
- Long-term exposure to smaller amounts of chlorine gas may contribute to pulmonary disease.
- The current US legal limit for occupational exposure to chlorine gas enforceable by the Occupational Safety and Health Administration (OSHA) is 0.5 ppm averaged over an 8-hour day, not to exceed 1.0 ppm for more than 15 minutes at a time.[36]

Complications

- Short-term effects of acute exposures of chlorine gas
  - Smokers and those with asthma are most likely to demonstrate persistence of obstructive pulmonary defects.[3]
  - Within 3-5 days, after the sloughing off of the mucosa, oozing areas become covered with mucopurulent exudate. This can result in chemical pneumonitis, often complicated by secondary bacterial invasion.

- Residual effects following acute exposures of chlorine gas
  - Long-term follow-up studies of acute human exposures to chlorine gas provide conflicting data on the potential for long-term adverse effects from short-term chlorine exposure.
  - In one study, after 2 years of follow-up, research subjects displayed decreased vital capacity, diffusing capacity, and total lung capacity with a trend towards higher airway resistance.[37] This suggests that persistent dose-related lung function deficits may occur following acute chlorine gas exposure.
  - Other studies demonstrated no consistent pattern of pulmonary function deficits following acute exposure.[38,26,39,40]
  - Jones et al found that long-term sequelae after acute chlorine gas exposure were more affected by cigarette smoking than by the chlorine gas exposure.[3]
  - Although no definite conclusion can be drawn concerning the long-term effects of an acute chlorine gas exposure, findings point to an increased nonspecific airway responsiveness that may persist. Following an acute exposure, some patients displayed eventual repair of injured pulmonary epithelium with fibrosis.[41] Bronchiolitis obliterans and emphysema have been described in patients following acute exposures.

- Reactive airway dysfunction syndrome (RADS), or irritant-induced asthma, is a variant of occupational asthma that occurs in individuals who are acutely exposed to high concentrations of an irritant product and develop respiratory symptoms in the minutes or hours that follow. They develop persistent bronchial hyperresponsiveness after the inhalational incident.[42] A similar pathology may occur with repeated exposures.[43]
Prognosis

- Resolution of pulmonary abnormalities in most individuals occurs over the course of one week to one month following exposure.

Patient Education

- For excellent patient education resources, visit eMedicine’s Bioterrorism and Warfare Center. Also, see eMedicine’s patient education articles Chemical Warfare and Personal Protective Equipment.

Miscellaneous

Medicolegal Pitfalls

- Early discharge (Pulmonary edema may present after several hours.)
- Failure to consider co-inhalants
- Failure to manage the airway aggressively in a patient with laryngospasm

Special Concerns

- The following populations are at higher risk of severe reaction and progression to respiratory failure than other populations.
  - Children and elderly individuals
  - Those with underlying respiratory or cardiovascular disease
  - Smokers

Multimedia


References


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