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TOXICOLOGY CASE FILES

Case Files of the University of California San Francisco Medical Toxicology Fellowship: Acute Chlorine Gas Inhalation and the Utility of Nebulized Sodium Bicarbonate

John E. Vajner III · Derrick Lung

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Case Presentation

On a sunny California day in August, the San Francisco Poison Control Center (PCC) received a call from paramedics that a previously healthy 3-year-old girl had possibly been exposed to chlorine gas at a neighborhood swimming pool. The Fire Department later confirmed that both a 10–16 % sodium hypochlorite solution and a 15 % hydrochloric acid solution were used for pool cleaning that day. The patient was sitting near an outflow jet in the children's pool, and her mother noticed a sudden increase in bubbles from the jet accompanied by a noxious odor. The mother promptly removed the patient from the pool and estimated an exposure time of approximately 45 s.

What Are the Characteristics of Chlorine Gas?

A member of the halogen group, chlorine primarily exists in nature as the chloride ion, forming numerous natural salts and comprising 1.9 % of the mass of the world's oceans [1]. Under standard conditions of temperature and pressure, elemental chlorine is a diatomic molecule in gaseous form, displaying a yellow–green color. This characteristic coloring was the inspiration behind the naming of chlorine in 1810 by Sir Humphrey Davy from the Greek *chlōros*, meaning yellow–green [2]. Chlorine gas is approximately 2.5 times heavier than air, and it has intermediate reactivity with water —characteristics that have important implications in its toxicity.

J. E. Vajner III (✉)
Department of Emergency Medicine, UCSF-Fresno,
155 N. Fresno Street,
Fresno, CA 93701, USA
e-mail: jvajner@fresno.ucsf.edu

D. Lung
Medical Toxicology Fellowship, Department of Emergency Medicine, University of California San Francisco,
San Francisco, CA, USA

In What Settings Do Exposures to Chlorine Gas Occur?

Exposures to chlorine gas commonly occur in one of four settings: in-home cleaning product misadventures, swimming pool chlorination reactions, industrial accidents, and intentional exposures with intent to harm, i.e., chlorine as a chemical weapon. According to data from the American Association of Poison Control Centers (AAPCC), there were 5,945 exposures to chlorine gas reported to domestic poison centers in 2009. Of these, 1,266 (21 %) were the result of mixing an acid-containing household cleaner with sodium hypochlorite (bleach), while the sources of the remaining exposures were not given [3]. Acid-containing household cleaners include: glass and window cleaners, toilet bowl cleaners, concrete and grout cleaners, drain cleaners, and lime, rust, and calcium removers. The implicated acids include gluconic, lactic, glycolic, sulfamic, phosphoric, citric, tannic, oxalic, hydrochloric, and sulfuric acids.

Several different compounds in various combinations are used to chlorinate pools. These pool-cleaning agents produce chlorine gas through spontaneous decomposition or by mixture with water or other cleaning compounds. Case reports of chlorine gas exposures include direct inhalation of chlorine gas from chemical containers, swimming during rapid injection of large quantities of chlorinating agents into pool lines, and mixing chlorinating agents with water in preparation for addition to the pool [4, 5].

Industrial exposures during production, storage, and transportation of chlorine also occur, since over 15 million tons of chlorine is produced each year in the USA.

Chlorine is used in the manufacturing and processing of many products, including plastics, rubbers, paper, pharmaceuticals, pesticides, cosmetics, disinfectants, batteries, antifreeze, and adhesives. Many safeguards are employed to prevent chlorine-related accidents, but its reactivity with ubiquitous compounds (such as water, steam, metals, and flammable gases) makes industrial exposures potentially devastating and difficult to prevent [6–8].

Two trains collided in Graniteville, SC, in 2005. The collision released 90 tons of chlorine gas, resulting in 9 fatalities, over 500 physician visits, and the evacuation of over two thirds of the town's 7,000 residents for several days. In 2007 in Tacoma, WA, 900 lb of chlorine gas was accidentally released during transfer from a rail car to storage containers. Twenty-five people were injured, and the accident resulted in the temporary closure of the Port of Tacoma, the seventh largest container port in North America [9].

What Decontamination Procedures and Personal Protective Equipment Are Required on Scene?

Scene safety is of paramount importance in cases of large-scale chlorine gas release. The 2007 Tacoma incident resulted in the release of 900 lb of chlorine gas. During the course of cleanup, the wind shifted, exposing 12 first responders to the gas. This example illustrates the innate volatility of accident sites. Combining this unpredictability with the potential for high gas concentrations, prolonged exposure times, and persistent sources of gas, the necessity of robust safety precautions becomes self-evident. According to the Occupational Health and Safety Administration, personal protective equipment (PPE) in cases of irritant gases should consist of a positive pressure ventilation system plus either a totally encapsulating chemical-protective suit or hooded chemical-resistant clothing, corresponding to Level A and Level B PPE, respectively [6]. The decision whether to use Level A or B is determined by the potential for skin irritation. Chlorine gas is nearly nonreactive with skin at concentrations encountered in even the worst accidents; thus Level B, protection is likely sufficient.

However, in the usual residential or poolside exposure, PPE is unlikely to be needed, as most of the gas will have dissipated by the time first responders arrive. Furthermore, on-scene decontamination in most cases consists only of removal of the patient from the incident site and removal of contaminated clothing. In cases of ocular irritation, copious irrigation and contact lens removal are indicated.

Case Continuation

Paramedics reported that, on scene, the girl vomited once and was in respiratory distress with wheezing. En route to the hospital, paramedics made contact with the PCC and delivered 15–30 min of continuous nebulized albuterol by non-rebreather mask. Upon arrival to the emergency department (ED), the patient's vital signs were: temperature, 36.4 °C; respiratory rate, 30/min; heart rate, 163/min; blood pressure, 91/71 mmHg; and oxygen saturation mid-90s on room air. On initial examination, the patient had cough, tachypnea, increased work of breathing without retractions or wheezes, and a sedate, glassy-eyed look. At this time, the patient's chest X-ray revealed mild perihilar peribronchial thickening, reportedly consistent with acute or chronic bronchitis.

What Is the Pathophysiology of Chlorine Gas-Mediated Inhalational Injury?

The toxic effects of chlorine gas are mediated by the products of chlorine's reaction with water on the mucosal surfaces of the oro- and nasopharynx, the conjunctivae of the eyes, and on the epithelial surfaces of the lungs. A strong oxidizing agent, chlorine reacts with water in the following redox reaction, creating both hypochlorous and hydrochloric acids:

$$H_2O + Cl_2 \leftrightarrow HCl + HOCl \leftrightarrow 2HCl + O^-$$

As illustrated above, hypochlorous acid further decomposes into hydrochloric acid and an oxygen free radical. All of these toxic products contribute to lung damage from chlorine inhalation.

HCl has been shown to react with S–S bonds, hydroxyl groups, and amide groups on cell surface proteins. Similarly, HOCl has been shown to react with S–S bonds, sulfhydryl groups, and amide groups [10, 11]. The results of such interactions are interference with cellular glucose uptake, loss of cellular K^+, cell swelling, inhibition of glycolysis, and ultimately cell lysis [12]. Serial bronchial biopsies were performed on a patient who experienced wheezing, throat irritation, and chest pain after exposure to chlorine gas. Biopsies performed from 3 days to 5 months after exposure revealed persistent desquamation of epithelium, with early biopsies showing subepithelial hemorrhages and inflammatory infiltrates [13].

Water solubility is another characteristic of chlorine gas that modulates its toxicity. Highly water-soluble gases, such as ammonia, are absorbed in the proximal airways, exerting the brunt of their toxic effects on proximal airways and mucosal surfaces. Relatively water-insoluble gases, such as phosgene, penetrate deep into the lungs without being absorbed by proximal mucosal surfaces and are primarily toxic at distal sites. Chlorine gas, having intermediate water solubility, interacts with both proximal and distal sites, producing mucosal irritation, airway irritation, and

potentially, alveolar pathology. One study showed that greater than 90 % of inspired chlorine gas is absorbed before reaching the hypopharynx when low concentrations are inhaled [14]. However, deeper penetration would be expected with larger tidal volumes and higher gas concentrations.

What Is the Typical Presentation of the Patient with Chlorine Gas Exposure?

The most common presenting complaints are cough and dyspnea, followed by sore throat, chest pain, wheezing, eye and nose irritation, and nausea [15, 16]. Physical exam findings vary depending on exposure severity but most commonly consist of wheezing, rales, decreased breath sounds, tachypnea, and increased work of breathing. In their 2009 study of 25 young, male soldiers exposed to chlorine gas on a military base, Cevik et al. found that 48 % of patients had wheezing, rales, or decreased breath sounds [15]. In 2002, Güloğlu et al. described a cohort of 106 people exposed to chlorine gas in Turkey, of which 28 % had abnormal pulmonary physical findings—primarily wheezing [17]. Among these two relatively large cohorts, only six patients total were reported to have hypoxia, and only six had abnormal chest radiographs. A 1998 account of 13 children exposed to chlorine at public pools reported that 5 of 13 were hypoxic while breathing ambient air on presentation [5].

Chest radiography is typically negative on presentation, but may reveal pulmonary edema. Initial arterial blood gas measurement may show hypoxia, but is more typically normal. Pulmonary function testing performed during hospitalization can show obstructive, restrictive, or combined-pattern dysfunction [34, 35].

Despite the dramatic presentations of patients described in smaller cohorts and case reports, the majority of reported exposures to chlorine gas result in little or no harm. Of the 5,945 cases reported to the AAPCC in 2009, sufficient information was gathered to classify short-term outcomes in 3,440 of these cases. There were no deaths, 13 severe outcomes (life threat or residual disability), 923 moderate exposures (required treatment), and 2,504 cases with mild or no pathologic effect. Of all reported exposures, 2,655 were evaluated in hospital [3]. In 2004, Evans reported that of 21 published reports of accidental chlorine gas exposure with 3,069 total cases, there were 18 deaths [4].

In 2005, a Graniteville, SC, train derailment released over 40 tons of chlorine gas. Van Sickle et al. studied the resulting cohort of 71 hospitalized patients and found that hypoxia on presentation, a decreased PaO_2/FiO_2 ratio, and acid–base derangements were associated with increased length of hospitalization [19].

What Is the Standard Therapy for Chlorine Inhalation Injury?

Standard therapy for chlorine inhalation is largely supportive and consists of decontamination, humidified supplemental oxygen, and nebulized β-agonists for bronchospasm. Other potentially beneficial therapies, such as corticosteroids (both inhaled and systemic) and inhaled nebulized sodium bicarbonate, are less established. *Goldfrank's Toxicologic Emergencies*, a common medical toxicology reference, acknowledges these alternative therapies, but refrains from making recommendations regarding their use [20].

Case Continuation

The patient received one treatment of nebulized albuterol/ipratroprium bromide solution in the ED. After initial treatments by EMS and ED staff, the patient had improvement in both her appearance and respiratory status, and the treatment team decided to admit the patient to a floor bed for observation. However, over the ensuing 2 h, the patient's respiratory condition worsened. She again developed respiratory distress with retractions and required oxygen by non-rebreather mask, with which she had an oxygen saturation of 96 % (roughly corresponding to a PaO_2 of 80 Torr) and respiratory rate of 64/min. A second chest X-ray ordered during this functional decline revealed frank pulmonary edema. At this point, the pediatric ICU was contacted for admission, and the ED attending physician contacted the PCC for recommendations.

Are Steroids Beneficial in the Treatment of Chlorine Gas Inhalation?

Corticosteroids have been suggested as a therapeutic adjunct in chlorine gas inhalation. They are postulated to abate the inflammatory response, countering the chlorine-mediated decrease in lung compliance and gas exchange, and to be particularly useful in patients with underlying reactive airway disease. However, while there are good data from studies in pigs to suggest effectiveness of this therapy, there is only anecdotal evidence in humans [21–24].

Wang et al. exposed 24 adult pigs via tracheotomy to chlorine gas at a concentration of 400 ppm for 15 min. The pigs were then treated with inhaled budesonide, IV betamethasone, or placebo. They found statistically significant improvements in arterial oxygen tension, pulmonary vascular resistance, and airway pressure in both the inhaled and IV steroid groups [22]. A recent 2011 review of steroid use in inhalational lung injury (not specific to chlorine gas) reported that corticosteroids may have a beneficial effect in

nonsevere acute lung injury caused by water-soluble gases when initiated immediately after exposure. However, the review concluded that data on the efficacy of corticosteroids for acute lung injury due to water-soluble gases are inconclusive given the lack of controlled studies and the unclear indications for administering corticosteroids [25]. The utility of corticosteroids for acute chlorine gas inhalation is likewise questionable given currently available data.

Is Nebulized Sodium Bicarbonate Beneficial in the Treatment of Chlorine Gas Inhalation?

Nebulized sodium bicarbonate for chlorine inhalation injury was first suggested by Done in his 1976 review of toxic inhalations [26]. Done's recommendation was based on the supposition that chlorine-related lung injury was mediated by acid production on the surface of the pulmonary epithelium. Since that time, the literature addressing the question of nebulized sodium bicarbonate in chlorine inhalation has grown significantly. Data in humans come from two case reports, four observational studies, and one prospective, randomized, controlled study [15–17, 27–30].

The first published case report describing the use of nebulized sodium bicarbonate describes three male patients, aged 19 to 20 years, who were exposed to chlorine gas from a malfunction of the chlorination system of an indoor pool. All three men presented with throat pain, chest pain, dyspnea, nausea, and coughing. They presented within 10 min of developing symptoms and were treated only with 4 cc of 3.75 % nebulized sodium bicarbonate solution. The patients' cough, shortness of breath, and respiratory distress completely resolved [27].

Douidar reported a 7-year-old girl who developed respiratory symptoms after opening a can of chlorine tablets. She was in marked respiratory distress with tachypnea, wheezing, and hypoxia after treatment with nebulized albuterol. Subsequently, she was treated with 4.25 mL of 3.75 % nebulized sodium bicarbonate solution over 20 min, and her symptoms quickly resolved [28].

Four observational studies have also examined the utility of nebulized sodium bicarbonate for treatment of chlorine inhalation toxicity. Hurlbut et al. treated 14 patients with 8.4 % nebulized sodium bicarbonate solution after chlorine inhalation and observed resolution of chest pain, throat irritation, and cough. Importantly, the authors did not observe resolution of bronchoconstriction [29].

In 1994, Bosse made similar observations in 86 cases of chlorine inhalation treated with 5 mL of 5 % nebulized sodium bicarbonate solution. These cases were reported to the Kentucky Regional Poison Center by 49 different medical facilities over a 2-year period. Bosse noted that reporting of response to therapy was nonuniform and that conclusions about efficacy were difficult to draw but that, subjectively, at least some patients had a favorable response to nebulized sodium bicarbonate therapy [16].

An observational study by Güloğlu et al. dubiously concluded that nebulized sodium bicarbonate was an "inadequate supportive therapy" for treatment of chlorine inhalation injury. This paper broadly describes the clinical features and treatment of 106 people treated at four different hospitals for exposure to chlorine gas in southeastern Turkey. An irregularity in the paper makes it unclear whether the number of patients treated with nebulized sodium bicarbonate was one or two. Additionally, the paper does not compare outcomes between treatment groups. For these reasons, it is unclear how study authors drew this oft-cited conclusion regarding use of nebulized sodium bicarbonate [17].

In a 2009 study, 25 young, male soldiers were exposed to chlorine gas during cleaning activities due to inappropriate mixtures of cleaning agents. All patients were treated with nebulized salbutamol, and 19 of 25 were also given inhaled budesonide and 4 mL of 3.75 % nebulized sodium bicarbonate solution. There was no difference in outcomes between the 19 treated with budesonide and sodium bicarbonate and the 6 who were not [15].

Only one prospective study has tested the utility of nebulized sodium bicarbonate for chlorine inhalation. In a 2006 randomized, double-blind, placebo-controlled study, 44 subjects were treated with nebulized salbutamol, IV prednisolone, and either nebulized placebo or 4 mL of 4.20 % nebulized sodium bicarbonate solution. Subjects were enrolled over a 1-year period if they presented to the emergency department with wheezing after acute exposure to chlorine gas and had no known history of pulmonary disease. Pulmonary function tests were performed before and after treatment. The only statistically significant difference between groups was an increase in FEV_1 in the bicarbonate group at 240 min (2.9 versus 2.4 L). Both groups reported an improvement in quality of life after treatment, as measured by the Acute Asthma Life Quality Survey, but there was no significant difference between the groups [30]. There were no clinically apparent adverse reactions to nebulized sodium bicarbonate in any case reports or studies.

What Are Long-Term Outcomes After Chlorine Gas Inhalation, and Are There Predictors of Severe Outcomes?

The great majority of patients with acute exposures to chlorine gas appear to have no long-term residual pulmonary deficits. Bonetto et al. followed ten children exposed to chlorine gas at a swimming pool. All children had respiratory distress initially with decreased FVC (mean 51 % predicted) and FEV_1 (mean 51 % predicted). However, all children had return to baseline PFTs within 15 days of exposure, with no residual pulmonary deficits at 15 months [31]. Chasis et al. followed 418 patients exposed to chlorine

gas in a New York subway tunnel, 33 of whom were severely affected, and found no residual effects at 16 months post-exposure [32]. Weill et al. studied 12 individuals who were among the most severely affected after a major chlorine accident. None had residual pulmonary deficits at 7 years post-exposure [33]. Two other large cohorts of acutely chlorine-exposed individuals revealed pulmonary function abnormalities in 121 of 211; all abnormalities completely resolved within 1 month [34, 35].

However, there is a poorly characterized risk for long-term health effects from acute chlorine gas exposure. Five months following the massive chlorine gas release at Graniteville, 94 of the over 600 persons affected by the chlorine gas release responded to a CDC questionnaire. Of these persons, 49 (52 %) reported a continued need for medications for unspecified chlorine-related health effects [36]. Additionally, there are several case reports that describe patients with one-time exposures to chlorine gas who developed reactive airway dysfunction syndrome that persisted for years after exposure [18, 37–41]. All patients reported were current smokers, former smokers, had a history of atopy, or had a history of childhood asthma. These data are anecdotal, but they suggest that a medical history of atopy, asthma, or smoking may portend a less-favorable long-term prognosis. Airway hyperresponsiveness has also been implicated as a risk factor for severe acute sequelae after acute chlorine exposure. D'Alessandro et al. exposed five subjects with airway hyperresponsiveness (determined by prestudy inhaled methacholine challenge) and five without hyperresponsiveness to 1.0 ppm of chlorine gas for 60 min. The hyperresponsive study participants had a significantly greater decrease in FEV_1, −520±383 versus −180 ±84 mL [42]. Low-level chronic exposure to chlorine gas or repeated higher-level exposure might also increase risk of developing long-term pulmonary deficits, including obstructive or restrictive disease and/or reactive airways [4].

What Is the Potential for Weaponization of Chlorine Gas?

The utility of weaponized chlorine gas is widely recognized, and the intentional release of chlorine gas is the subject of one of the Department of Homeland Security's 15 "National Planning Scenarios" [43]. The first documented use of chlorine gas as a chemical weapon was in 1915 during the First World War in Ypres, Belgium. In this attack, allied forces were exposed to high concentrations of the gas, resulting in hundreds (perhaps thousands) of deaths and several thousand incapacitations and hospitalizations [4, 44]. In 2007, there were numerous attacks in Iraq using chlorine gas. Most of these attacks involved chlorine tanker trucks armed with explosives [9]. The two deadliest attacks killed 30 and 45 people [45, 46]. Another series of three attacks within a 3-h period injured over 350 people [47].

Have Any Specific Triage Guidelines Been Developed for Large-Scale Chlorine Gas Exposures?

The authors could not locate any such guidelines. Experience from domestic accidents suggests that exposed individuals will largely self-triage in the field, meaning those who have minimal or no symptoms will typically escape the scene and further exposure. Remaining victims will have likely suffered more severe injury, and their triage should be primarily based on current symptomatology, as patients who are asymptomatic or mildly symptomatic initially are not expected to have severe delayed symptoms. Triage considerations should also include assessment of number of injured, coordination of multiple hospitals, evaluation of wind speed and direction for establishing safe zones and warning those downwind, and perhaps an assessment for comorbidities and medical history (such as pulmonary disease, atopy, heart disease, etc.), which may indicate patients at higher risk for prolonged symptoms and exacerbations of preexisting conditions.

Case Conclusion

Upon arrival to the pediatric ICU, the patient had retractions and was still receiving O_2 at 15 L/min by non-rebreather mask. The patient again received nebulized albuterol without benefit. Three hours after initial presentation to the ER, on the recommendation of the PCC, the patient was given a nebulized mixture of 3 mL of 8.4 % sodium bicarbonate solution and 2 mL of normal saline, resulting in near-immediate improvement in work of breathing, tachypnea, and oxygen saturation. The patient was given IV corticosteroids 1 h after nebulized sodium bicarbonate. Twelve hours after administration of nebulized sodium bicarbonate, the patient was breathing room air. Upon further discussion with the patient's family, PICU doctors discovered that the patient had a history of wheezing with upper respiratory infections and also a strong family history of atopy.

Conclusion

Acute chlorine inhalation remains a relatively common toxicologic emergency, and it is important to understand the epidemiology, clinical course, and treatment of such exposures. Nebulized albuterol, humidified oxygen, and decontamination remain the mainstays of treatment. Nebulized sodium bicarbonate and corticosteroids have potential benefit given the pathophysiology of disease and the proclivity of patients with underlying reactive airway disease to have severe reactions. No adverse reactions to either therapy have been reported in this setting. Despite the sometimes

dramatic presentations of patients with exposures to chlorine gas, most recover without long-term sequelae.

Conflict of Interest The authors have no conflicts of interest.

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