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Civilian exposure to chlorine gas: A systematic review

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ABSTRACT

Introduction: Halogen pulmonary irritants (HPIs) are volatile liquids that directly damage the respiratory mucosa. Chlorine is readily available in large volumes as an industrial chemical and has a significant potential for accidental or deliberate release. We conducted a systematic review to determine the clinical features; treatment and long-term sequelae of civilian chlorine gas exposure.

Methods: A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. Medline; Ovid and Google Scholar databases were searched from 1966 to January 2017. A database of relevant papers was compiled and descriptive statistics used to summarise the data.

Results: Thirty-six papers describing 37 incidents involving 1566 individual acute exposers to chlorine gas were identified. The most common reported features were cough (29%), dyspnoea (22%), sore throat (16%), eye features (12%) and excessive sputum or haemoptysis (7%). Acute management included high-flow oxygen (32.8%); steroids (28.4%); bronchodilators (28.2%) and ventilation (2.3%). Nine deaths (0.6%) were reported. Follow-up data available in 60% of cases; full recovery was reported in 90% of cases where data was available.

Discussion: Acute chlorine gas exposure in civilian incidents presented with acute respiratory features and irritation of the eyes and throat. The development of pulmonary oedema or ARDS was relatively rare when compared to military experience in the First World War.

1. Introduction

Simple halogen pulmonary irritants (HPIs) are volatile, diatomic, molecules that directly damage the respiratory mucosa in a dose-dependent manner (Miller et al., 2000) through the formation of oxidizing solutions (Barrow et al., 1977). Chlorine is available worldwide in large volumes as a household and industrial chemical. It readily forms a true gas, due to its high vapour pressure, and has significant potential for accidental or deliberate release, as observed in conflicts from the First World War to the current Syrian conflict (Padley, 2016). As such, HPIs are likely to represent an enduring threat to both civilian and military populations in future conflicts or acts of terrorism; in addition to the hazard from accidental domestic or industrial exposure.

The odour of chlorine gas can be detected at concentrations of 0.1–0.3 ppm. At concentrations less than 15 ppm, chlorine is a mucosal membrane irritant but at concentrations more than 30 ppm may cause symptoms; of cough, dyspnoea and retrosternal chest pain (White and Martin, 2010). Concentrations greater than 50 ppm directly damage the bronchial tree and lung parenchyma, resulting in clinical features of pneumonitis and pulmonary oedema (Winder, 2001). At concentrations greater than 400 ppm death may occur after 30 min exposure; death may occur within minutes following exposure to concentrations exceeding 1000 ppm (White and Martin, 2010). Early deaths, within four hours of exposure, were noted to have cardiomegaly reported at autopsy in causalities from an accidental release of chlorine (Van Sickle et al., 2009). Seven (87%) of the deceased were described has having pre-existing cardiomegaly and the deaths were attributed to asphyxia (Van Sickle et al., 2009).

Military cohort studies from the First World War reported a high incidence of acute respiratory features but low mortality rates, typically less than 5%, and relatively low chronic respiratory symptoms (Das and Blanc, 1993). Exposure to chlorine, typically disseminated from high-pressure cylinders, in previous conflicts was associated with irritation of the eyes, upper airways, central airway irritation and pulmonary oedema (Winder, 2001), a feature attributed to its intermediate solubility and reactivity (Squadrito et al., 2010). Casualties usually developed non-cardiogenic pulmonary oedema around 12 h post-exposure, with death occurring at 24 to 48 h (White and Martin, 2010). The relevance of historical military data to contemporary chemical incidents is uncertain. Military casualties often had traumatic injuries in addition to chemical exposure and, in many cases, the identity of the chemical agent either unknown or involved a mixture of chemicals.

There are no specific antidotes or pre-exposure countermeasures for chlorine toxicity in humans; current treatment is supportive. Several

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potential therapeutic approaches have recently been considered. Animal models of chlorine-induced acute lung injury suggest a potential role for beta-2 adrenoreceptor agonists in pigs; inhaled corticosteroids in pigs (Wang et al., 2004) and rats (Demnati et al., 1998); the endothelin receptor antagonist, tezosentan, in pigs (Wang et al., 2006); transient receptor potential vanilloid 4 (TRPV4) inhibition in mice (Balakrishna et al., 2014) and metalloprotease inhibition in mice (Villalta et al., 2014). The efficacy and safety of these therapies, specifically the role of corticosteroids (de Lange and Meulenbelt, 2011), in the treatment of human chlorine gas casualties are unknown.

We conducted an open-source systematic review to determine the clinical features; treatment and long-term sequelae following acute exposure of civilians to chlorine gas to guide the clinical and public health management of future incidents.

2. Methodology

A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology, a checklist to improve the reporting of systematic reviews (Moher et al., 2009). The Medline; Ovid and Google Scholar databases were searched from January 1966 to January 2017 using the search terms "*pulmonary irritant*", "*poison** or *toxic** or *fatal** or *inhal**" and "*halogen*" or "*chlorine*". The search was limited to human data. Papers were screened by both authors and included if the abstracts were available in English; pertained to acute chlorine gas exposure; details of the source of exposure was available and a description of clinical features present. Duplicate reports of the same incident were excluded as were post-mortem reports. Review articles were excluded, unless the article also contained a case-report or case-series. Chronic exposures; exposures to mixtures or unidentified chemicals were excluded. The references of identified papers were reviewed for further papers. A database of relevant papers was compiled and descriptive statistics used to summarise the data. Confidence intervals of proportions were calculated using the modified Wald method (Agresti and Coull, 1998). Chi-squared was used to compare proportions. A p-value of less than 0.05 was considered statistically significant.

3. Results

Three hundred and forty-six papers were retrieved using the search criteria. Of these, 319 were excluded: 261 did not relate to acute chlorine exposure or contained insufficiently details; 47 were not available in the English language; seven were review articles and four were mechanistic studies not relating directly to chlorine exposure. Fourteen further papers were identified through examination of references, of which five were excluded. A total of 36 papers were included in the review (Table 1) (Van Sickle et al., 2009; Beach et al., 1969; Chester et al., 1977; Gapany-Gapanavicius et al., 1982; Fleta et al., 1986; Vinsel, 1990; Heidemann and Goetting, 1991; Moore and Sherman, 1991; Pino et al., 1993; Deschamps et al., 1994; Myers, 1997; Agabiti et al., 2001; Güloğlu et al., 2002; Traub et al., 2002; Kilburn, 2003; Parimon et al., 2004; Akdur et al., 2006; Vohra and Clark, 2006; Bonetto et al., 2006; Kanne et al., 2006; Grasemann et al., 2007; Ngo et al., 2007; Howard et al., 2007; Centers for Disease Control and Prevention (CDC), 2007, 2011, 2012; Babu et al., 2008; Sever et al., 2009; Cevik et al., 2009; Kose et al., 2009; Mohan et al., 2010; Li et al., 2011; Vajner and Lung, 2013; Kim et al., 2014; Bellenger and Frizzi, 2014; Carpenter et al., 2016). All were case-series or case-reports.

A total of 1566 individual exposures to chlorine gas were identified, of which clinical features were reported in 1565 individuals, one case documented two exposures in a single individual (Babu et al., 2008). Eight hundred and sixteen cases were male and 750 female, p = 0.1. The median average age of exposed individuals was 24 years of age, ages of individuals ranged from 4 months to 76 years of age. The presence of pre-existing conditions, such as asthma, or exposure to other confounders, such as tobacco smoke, were inconsistently reported.

Table 1
Case reports and case-series of civillian chlorine exposures.

Reference	Year	Incident type	Cases
17	1969	Industrial	7
18.	1977	Industrial	2
19	1986	Industrial	76
20	1990	Swimming pool	3
21	1991	Swimming pool	1
22	1991	Industrial	1
23	1993	Swimming pool	1
24	1994	Domestic	1
25	1997	Swimming pool	1
26	1998	Domestic	2
27	2001	Swimming pool	260
28	2002	Industrial	106
29	2002	School	1
30	2003	Domestic	13
31	2004	Swimming pool	1
32	2006	Domestic	1
33	2006	Swimming pool	1
34	2006	Swimming pool	10
35	2006	Swimming pool	1
36	2007	Swimming pool	18
37	2007	Swimming pool	36
38	2007	Domestic	1
39	2007	Swimming pool	24
40	2008	Swimming pool	1
41	2009	Industrial	39
6	2009	Industrial	79
42	2009	Domestic	25
43	2009	Domestic	1
44	2010	Swimming pool	64
45	2011	Swimming pool	2
46	2011	Industrial	27
47	2012	Industrial	545
48	2013	Swimming pool	1
49	2014	Industrial	211
50	2014	Industrial	1[a]
51	2016	Industrial	1

[a] One individual with two, separate, acute exposures to chlorine gas.

Exposure to chlorine gas occurred through industrial or transportation accidents in 1097 cases (70%); 425 cases related to swimming pools (27%) and forty-four cases involved the generation of chlorine gas from reactions between sodium hypochlorite cleaning agents (3%). Information on the estimated dose, in terms of both chlorine concentration and duration of exposure, were not consistently reported.

A total of 2407 clinical features were reported (percentage ± 95% confidence interval): cough (29% ± 2%); dyspnoea (22% ± 2%); sore throat (16% ± 1%); eye irritation (12% ± 1%); excessive sputum or haemoptysis (7% ± 1%); wheeze (4% ± 1%); nausea or vomiting (6% ± 1%); headache (2.2% ± 1%) and non-cardiogenic pulmonary oedema/acute respiratory distress syndrome (ARDS) (0.4% ± 0.2%). Diagnostic criteria for pulmonary oedema or ARDS was rarely reported. Complications of chlorine exposure included 9 deaths (0.6%), all relating to the Graniteville transportation incident (Van Sickle et al., 2009); four cases involving spontaneous pneumomediasternum (0.3%) (Gapany-Gapanavicius et al., 1982; Akdur et al., 2006; Li et al., 2011) and a single case complicated by an acute myocardial infarction and acute stroke (Kose et al., 2009).

One thousand, five hundred and eighty-four treatment modalities were reported: high-flow oxygen therapy (32.8%); corticosteroids (28.4%); nebulized beta2-adrenoreceptor agonists (28.2%); nebulized muscarinic antagonists (6.4%) and mechanical ventilation (2.3%). The dose; dose-intervals and clinical response of individual therapies were not consistently reported; neither was the ventilator type or settings. Systemic corticosteroid regimes included oral prednisolone, 1 mg/kg daily for four weeks (Parimon et al., 2004); intravenous hydrocortisone, 100 mg daily for two days, changed to oral hydrocortisone 45 mg for