Chlorine Countermeasures: Supplemental Oxygen Equals Supplemental Lung Injury?

We have experienced a renaissance in the use of chemical weapons during the past several years, especially within the Levant regions of the Middle East (1). Chlorine gas has been the most prolifically used chemical weapon there, and is also a common industrial chemical associated with accidental chemical intoxications across the globe (2). Although supportive-care strategies have been identified for chlorine-exposed patients, they have not been sufficiently studied. Hence, there are insufficient medical countermeasures available for the treatment of chlorine gas injuries. Such therapies are needed if we are to be prepared for the next chlorine accident or terrorist attack. Medical treatments need to be robust to be effective during mass casualty events when patients surge into hospitals and emergency departments (3), and should be easily available within all hospitals. There is a great need to identify such treatment strategies and study their differential efficacy. One simple countermeasure is supplemental oxygen administration.

However, it is well known that hyperoxia due to supplemental oxygen administration may cause additional lung injury (4, 5). Such lung injury is directly dependent on the severity of injury or impairment before treatment, the ventilation rate, the concentration administered, and the duration of oxygen supplementation. Therefore, it is medically reasonable to question whether supplemental oxygen administration as a medical countermeasure for chlorine intoxication may increase lung injury and illness within survivors. The work presented in this issue of the *Journal* by Okponyia and colleagues (pp. 107–116) was designed specifically to address that question (6).

The reported results of their study (6) suggest that oxygen supplementation treatment can help survival but cause additional oxidative injury. The data are clear: survival was better and many measures of disease severity were worse in the surviving study animals that received oxygen supplementation. But what do these data really mean? Do they definitively show that oxygen supplementation causes additional lung injury? No, they do not. So what else could explain these data?

Most toxicology studies expose animals to concentrations that do not cause significant mortality during the study period, after which all of the animals are killed and studied. The authors should be lauded for performing this important study using chlorine exposures at extremely high levels. Such high-dose studies are needed to maintain relevance to the increasingly frequent human exposures to high levels of chlorine during industrial accidents and in conflict zones around the globe.

Notably, only 42% of the exposed and untreated animals survived for 6 hours after exposure. In contrast, 89% of the exposed animals that were treated with oxygen supplementation survived throughout the full course of the study. Yes, these were all male Sprague-Dawley rats, which should limit variability among the study animals due to their common genetics. Yet there was variability in the responses to chlorine exposure in the untreated animals—some died and some survived.

Therefore, because only the animals that survived the study were studied at 6 hours postexposure, we must ask whether the surviving animals were representative of all of the exposed animals. Given that 89% of the oxygen-treated animals survived, it is reasonable to infer that the surviving animals represented the entire group (only one such animal did not survive). On the contrary, only 42% of the untreated animals survived the full study period. Thus, the comparability of that sample set to all of the untreated animals is suspect. Rather, it is quite likely that the untreated surviving animals were less susceptible to chlorine injury and were not representative of the full pool of untreated animals exposed to chlorine. Such differential survival would likely bias the results of the study such that the effects of the chlorine exposure within that group would be underreported, perhaps to the degree that the severe injury resulting in death would be unmeasured. It is implicit that the animals that did not survive had more severe disease, as suggested by the observation that all of the animals that did not survive experienced tonic seizures before their death and the surviving animals did not (6). The study of the surviving animals can only teach us about the injuries within the subset of animals that were uniquely resilient to chlorine injury and survived, not about all animals exposed to chlorine.

The authors conclude that the treatment group, which almost fully survived the study, exhibited more severe lung injury due to concurrent exposure to the hyperoxia resulting from oxygen supplementation. It is my contention that the group of animals that survived after oxygen treatment certainly included animals that would have died had they not been treated with oxygen. The study data strongly suggest that. Therefore, the group of exposed and treated animals that survived likely had disease as severe as the exposed animals that were untreated and did not survive 6 hours. In other words, the treated group overrepresented the disease severity by 47%, the difference in survival between the treated and untreated groups. Given that, including the statistical adjustments for the differential survival between study groups would be appropriate. This type of survivor bias is common in observational studies of workers (7), where it is known as the "healthy worker" or "harvesting" effect. We previously observed this within our chlorine cohort, which had fewer workers after a chlorine disaster because many were too sick to return to work (8).

Given these important caveats concerning the study by Okponyia and colleagues (6), what does it tell us about both chlorine injury and the effects that hyperoxia has on disease morbidity? In summary, this study tells us that oxygen supplementation will save lives after chlorine exposure, and that those who survive after oxygen supplementation will likely exhibit more severe injury than surviving untreated patients, because they would have died had they not received oxygen supplementation. This study clearly demonstrates the benefits of oxygen supplementation for survival up to 6 hours postexposure. Further studies are needed to better define the threshold at which oxygen

supplementation after chlorine injury becomes detrimental and should therefore be avoided. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Erik R. Svendsen, Ph.D.
Medical University of South Carolina
Charleston, South Carolina

References

1. Summerhill EM, Hoyle GW, Jordt SE, Jugg BJ, Martin JG, Matalon S, *et al*.; ATS Terrorism and Inhalational Disasters Section of the Environmental, Occupational, and Population Health Assembly. An official American Thoracic Society workshop report: chemical inhalational disasters. biology of lung injury, development of novel therapeutics, and medical preparedness. *Ann Am Thorac Soc* 2017; 14:1060–1072.
2. Hoyle GW, Svendsen ER. Persistent effects of chlorine inhalation on respiratory health. *Ann N Y Acad Sci* 2016;1378:33–40.
3. Christensen BE, Duncan MA, King SC, Hunter C, Ruckart P, Orr MF. Challenges during a chlorine gas emergency response. *Disaster Med Public Health Prep* 2016;10:553–556.
4. Kumar VH, Lakshminrusimha S, Kishkurno S, Paturi BS, Gugino SF, Nielsen L, *et al*. Neonatal hyperoxia increases airway reactivity and inflammation in adult mice. *Pediatr Pulmonol* 2016;51: 1131–1141.
5. Machado HS, Nunes CS, Sá P, Couceiro A, da Silva AM, Águas A. Increased lung inflammation with oxygen supplementation in tracheotomized spontaneously breathing rabbits: an experimental prospective randomized study. *BMC Anesthesiol* 2014;14:86.
6. Okponyia OC, McGraw MD, Dysart MM, Garlick RB, Rioux JS, Murphy AL, *et al*. Oxygen administration improves survival but worsens cardiopulmonary functions in chlorine-exposed rats. *Am J Respir Cell Mol Biol* 2018;58:107–116.
7. Brown DM, Picciotto S, Costello S, Neophytou AM, Izano MA, Ferguson JM, *et al*. The healthy worker survivor effect: target parameters and target populations. *Curr Environ Health Rep* [online ahead of print] 15 Jul 2017; DOI: 10.1007/s40572-017-0156-x.
8. Clark KA, Karmaus WJ, Mohr LC, Cai B, Balte P, Gibson JJ, *et al*. Lung function before and after a large chlorine gas release in Graniteville, South Carolina. *Ann Am Thorac Soc* 2016;13: 356–363.