Ozone toxicity - StatPearl

Introduction

Ozone occurs normally in a gas state as 3 atoms of oxygen (O_3) linked in a cyclic structure and is a by-product of water purification, bleaching and any process generating a spark or electric arc in the presence of oxygen. It is of course also found in the atmosphere with higher altitudes containing higher levels. It is found in the stratosphere where it absorbs various ultraviolet radiation and as an environmental air pollutant along with others such as sulfur dioxide and particulate matter. Ozone can also react with air and create nitrogen dioxide, another air pollutant, if it is improperly generated.[1,2]

In spite of this, ozone can be generated by medical devices for therapeutic purposes.[1] Potential medical applications of ozone therapy have a wide range including: 1) limiting post-operative pain after dental extraction when used as a gel, 2) repairing inner ear damage caused by acoustic trauma, 3) reducing coronary stent restenosis when applied as an autohemotransfusion, and 4) enhancing MRSA elimination in mediastinitis when used in conjunction with antibiotics.[3-6] Outside of medicine, ozone has been proposed for use in various settings such as in the pretreatment of textile wastewater.[7] While ozone itself can cause health troubles, it can also react with chemicals found in a multitude of products to lead to other potentially toxic substances such as formaldehyde.[8] Despite proponents for its use, and the potential applications, toxicity can occur even at environmental levels and may be related to cardiac, respiratory, and neurologic events.[9,10]

With the wide range of possible applications, and toxicity that can occur at environmental levels from within a home, research on ozone use and toxicity is likely to increase in the future.

Etiology

Exposure to ozone is most likely unintended and due to environmental sources both indoor and outdoor. Indoor exposure is decreased in residences with central air, likely due to the decreased exchange of indoor and outdoor air aside from the air that is filtered by the air conditioning unit. Despite its decreased presence, it can react with numerous indoor chemicals found in a variety of sources such as wood flooring, carpeting related products, and perfume to create potentially harmful compounds.[8]

The outside environment a person lives in is also a significant player in ozone exposure, potential toxicity, and overall cardiovascular and respiratory mortality. One large study of 95 communities in the United States found a statistically significant association between increases in ozone measured in parts per billion (ppb) and short-term daily mortality. This shows despite the common association, and its initial recognition, being southern California, that it plays a major role in public health.[11] Countries outside of the United States, such as South Korea and

Iceland, have also recognized the health impacts of ozone and the impact on public health.[9,12]

A difficult aspect of ozone toxicity is that it is not known what level or duration is tolerable, and that some may be more sensitive to it than others. One study found that pediatric asthmatics might be more sensitive to certain air pollutants such as ozone.[12] Another suggested that exposure to ambient levels of ozone may be enough to initiate inflammatory cascades of the respiratory tract.[13] Noting that, and the study involving 95 communities, it is plausible to say that ozone toxicity affects everyone to some degree and is dependent on multiple factors within and outside of our control.

Epidemiology

Risks associated with ozone toxicity are tough to determine due to the many factors, however one of the larger studies demonstrated that a 10-ppb increase in a communities ozone may be associated with a 0.52% risk of non-injury-related daily mortality the following week. Additionally, the same increase of environmental ozone may cause a 0.64% increase in mortality due to cardiovascular or respiratory causes.[11]

Aside from the general ozone toxicity, it has the potential to be iatrogenic and work related.[1,14] Despite that potential, little research and no case reports were found.

Toxicokinetics

Ozone is a potent oxidant that has the potential to be helpful or harmful like most other substances depending on the concentration, location, and duration of exposure. For example, ozone has shown to be beneficial in treating chronic limb ischemia and several kinds of skin infection. Conversely higher doses or more prolonged exposure to skin will lead to progressive depletion of antioxidant content in the stratum corneum.[16]

In discussing toxicokinetics it may be helpful to differentiate the exposure location, as the skin is somewhat tolerant (although chronic contact can be deleterious), while the respiratory system is essentially intolerant and can show harmful effects even at low ambient environmental concentrations. Tissue effects can be considered on the basis of ozone's specificity to certain compounds in addition to its low aqueous solubility and diffusibility. It is important to note that all possible pathways of injury are not likely known, and some known effects are not well understood yet.[15,16]

Toxic effects are considered to occur through free radicals and oxidation, or through radical-dependent pathways. Aside from generation of free radicals, ozone can deplete a tissue of specific compounds, such as antioxidants (tocopherols and ascorbate) in separated layers of skin (upper epidermis, lower epidermis, dermis).

Additionally, there is a noted increase of lipid and protein oxidation showing oxidative stress. Longer exposure to increased concentrations has shown an increase in cyclooxygenase-2, which is a proinflammatory marker.[16]

While effects are still related to oxidation and inflammatory pathways the respiratory tract has some mediation through interleukin-8 and growth-related oncogene-α.[17]

History and Physical

For most patients with effects that can be related to ozone toxicity the history will be non-specific, with findings dependent on the system involved, such as asthmatic symptoms in an asthmatic (who are particularly susceptible to ozone). Specific history of present illness events may only be found in patients undergoing unconventional medical therapies or individuals exposed in a work environment.

Symptoms themselves are largely related to the delivery method of exposure, concentration, and duration. Ozone has been delivered in many routes including, but not limited to, intravenous, intramuscular, topically, intra-articular, nasal, rectal and oral.[1]

Evaluation

Evaluation for ozone toxicity is similar to evaluation of any pulmonary irritant. Oxygen saturation monitoring should be implemented and also bedside spirometry. Providers should also consider arterial blood gas analysis and chest radiography as potential exposure to other pulmonary irritants should always be considered. An electrocardiogram should be performed as well in patients with or at risk for underlying cardiac disease.

Treatment / Management

No specific treatment is available for individuals exposed to ozone, though some have suggested that oral intake of vitamin E is beneficial to the chronic ambient exposure most experience.[18] Budesonide has been shown to inhibit the airway neutrophilic inflammatory response although it does not prevent functional impairment of the airway.[2]

Other Issues

Providers should be aware of the use of ozone therapy by holistic practitioners and ozone therapists. Although shown to be safe there have been instances with inexperienced individuals using ozone improperly, potentially causing harm. As with any drug, there is a therapeutic window depending on dosage. Unfortunately, there is a lack of financial support for conducting RCTs and much remains to be discovered about both therapeutic and toxic effects of ozone.

References

1. Bocci VA. Scientific and medical aspects of ozone therapy. State of the art. *Archives of medical research.* 2006;37(4):425-435.
2. Vagaggini B, Taccola M, Conti I, et al. Budesonide reduces neutrophilic but not functional airway response to ozone in mild asthmatics. *American journal of respiratory and critical care medicine.* 2001;164(12):2172-2176.
3. Gulmen S, Kurtoglu T, Meteoglu I, Kaya S, Okutan H. Ozone therapy as an adjunct to vancomycin enhances bacterial elimination in methicillin resistant Staphylococcus aureus mediastinitis. *The Journal of surgical research.* 2013;185(1):64-69.
4. Sivalingam VP, Panneerselvam E, Raja KV, Gopi G. Does Topical Ozone Therapy Improve Patient Comfort After Surgical Removal of Impacted Mandibular Third Molar? A Randomized Controlled Trial. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* 2017;75(1):51 e51-51 e59.
5. Barone A, Otero-Losada M, Grangeat A, et al. Ozone therapy protects from in-stent coronary neointimal proliferation. Role of redoxins. *International Journal of Cardiology.* 2016;223:258-261.
6. Yenigun A, Aksoy F, Dogan R, et al. Medical ozone therapy for the inner ear acoustic trauma. *International journal of pediatric otorhinolaryngology.* 2013;77(9):1512-1517.
7. Somensi CA, Simionatto EL, Bertoli SL, Wisniewski A, Radetski CM. Use of ozone in a pilot-scale plant for textile wastewater pre-treatment: physico-chemical efficiency, degradation by-products identification and environmental toxicity of treated wastewater. *Journal of hazardous materials.* 2010;175(1):235-240.
8. Weschler CJ. Ozone's Impact on Public Health: Contributions from Indoor Exposures to Ozone and Products of Ozone-Initiated Chemistry. *Environmental Health Perspectives.* 2006;114(10):1489-1496.
9. Carlsen HK, Forsberg B, Meister K, Gíslason T, Oudin A. Ozone is associated with cardiopulmonary and stroke emergency hospital visits in Reykjavík, Iceland 2003–2009. *Environmental Health.* 2013;12(1):28.
10. Malig BJ, Pearson DL, Chang YB, et al. A Time-Stratified Case-Crossover Study of Ambient Ozone Exposure and Emergency Department Visits for Specific Respiratory Diagnoses in California (2005–2008). *Environmental Health Perspectives.* 2016;124(6):745-753.
11. Bell ML, McDermott A, Zeger SL, Samet JM, Dominici F. Ozone and short-term mortality in 95 us urban communities, 1987-2000. *JAMA.* 2004;292(19):2372-2378.
12. Lee J-T, Kim H, Song H, et al. Air pollution and asthma among children in Seoul, Korea. *Epidemiology.* 2002;13(4):481-484.
13. Devlin RB, McDonnell WF, Mann R, et al. Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. *American journal of respiratory cell and molecular biology.* 1991;4(1):72-81.
14. Reed D, Glaser S, Kaldor J. Ozone toxicity symptoms among flight attendants. *American journal of industrial medicine.* 1980;1(1):43-54.

15. Kim DH, Kim YS, Park JS, et al. The Effects of On-site Measured Ozone Concentration on Pulmonary Function and Symptoms of Asthmatics. *J Korean Med Sci.* 2007;22(1):30-36.
16. Valacchi G, Fortino V, Bocci V. The dual action of ozone on the skin. *British Journal of Dermatology.* 2005;153(6):1096-1100.
17. Krishna M, Madden J, Teran L, et al. Effects of 0.2 ppm ozone on biomarkers of inflammation in bronchoalveolar lavage fluid and bronchial mucosa of healthy subjects. *European Respiratory Journal.* 1998;11(6):1294-1300.
18. Menzel D. Nutritional needs in environmental intoxication: vitamin E and air pollution, an example. *Environmental health perspectives.* 1979;29:105.