Ozone therapy: A clinical review

Authors: A. Elvis and J. Ekta
Date: January-June 2011
From: Journal of Natural Science, Biology and Medicine(Vol. 2, Issue 1)
Publisher: Medknow Publications and Media Pvt. Ltd.
Document Type: Report
Length: 2,979 words

Full Text:
Byline: A. Elvis, J. Ekta

Ozone (O [sub]3) gas discovered in the mid-nineteenth century is a molecule consisting of three atoms of oxygen in a dynamically unstable structure due to the presence of mesomeric states. Although O [sub]3 has dangerous effects, yet researchers believe it has many therapeutic effects. Ozone therapy has been utilized and heavily studied for more than a century. Its effects are proven, consistent, safe and with minimal and preventable side effects. Medical O [sub]3 is used to disinfect and treat disease. Mechanism of actions is by inactivation of bacteria, viruses, fungi, yeast and protozoa, stimulation of oxygen metabolism, activation of the immune system. Medication forms in a gaseous state are somewhat unusual, and it is for this reason that special application techniques have had to be developed for the safe use of O [sub]3 . In local applications as in the treatment of external wounds, its application in the form of a transcutaneous O [sub]3 gas bath has established itself as being the most practical and useful method, for example at low (sub-atmospheric) pressure in a closed system guaranteeing no escape of O [sub]3 into the surrounding air. Ozonized water, whose use is particularly known in dental medicine, is optimally applied as a spray or compress. Diseases treated are infected wounds, circulatory disorders, geriatric conditions, macular degeneration, viral diseases, rheumatism/arthritis, cancer, SARS and AIDS.

Introduction

Ozone (O [sub]3), a gas discovered in the mid-nineteenth century, is a molecule consisting of three atoms of oxygen in a dynamically unstable structure due to the presence of mesomeric states. The gas is colorless, acrid in odour and explosive in liquid or solid form. It has a half-life of 40 min at 20[degrees]C and about 140 min at 0[degrees]C. Its basic function is to protect humans from harmful effects of UV radiation. Ozone occurs at less than 20 [micro]g/m [sup]3 from the Earth's surface at concentrations that are perfectly compatible with life. Although O [sub]3 has dangerous effects, yet researchers believe it has many therapeutic effects. [sup][1],[2],[3] The beginning of precise medical O [sub]3 generators has only recently allowed the mechanisms, action and possible toxicity of O [sub]3 to be evaluated by clinical trials. [sup][2] Ozone has a capacity to oxidize organic compounds, [sup][4] and has well-known toxic effects on the respiratory tract when present in smog. [sup][5],[6] In medical use the gas produced from medical grade oxygen is administered in precise therapeutic doses, and never via inhalation, and advocates that it has excellent health benefits in dental caries, decrease blood cholesterol and stimulation of antioxidative responses, modifies oxygenation in resting muscle and is used in complementary treatment of hypoxic and ischemic syndromes. [sup][7],[8],[9],[10]

History of Ozone Therapy

Ozone therapy has been utilized and extensively studied for many decades altogether. Its effects are proven, consistent and with minimal side effects. Medical O [sub]3 , used to disinfect and treat disease, has been around for over 150 years. Used to treat infections, wounds and multiple diseases, O [sub]3 's effectiveness has been well-documented. It has been used to disinfect drinking water before the turn of the last century. Ozone was known to treat as many as 114 diseases. [sup][11] Ozone therapy has been in use since the 1800s and in 1896 the genius Nikola Tesla patented the first O [sub]3 generator in the US, later forming the 'Tesla Ozone Company." [sup][12] During the first world war (1914-18) doctors familiar with O [sub]3 's antibacterial properties, and with few other medical resources available to them applied it topically to infected wounds and discovered O [sub]3 not only remedied infection, but also had hemodynamic and anti-inflammatory properties. [sup][13] In the late 1980s, reports had emerged that German physicians were successfully treating HIV patients with 03-AHT (Autohemotherapy). There was then no pharmaceutical treatment for HIV and a pandemic was feared, so Canadian authorities authorized the study to test safety and efficacy of 03-AHT in AIDS patients. Ozone had shown promise in in vitro testing. Ozone was seen effective at disinfecting extracorporeal blood samples of HIV; unfortunately for AIDS patients, 03-AHT proved to be an in vivo ineffective treatment [sup][14],[15] [Table 1].{Table 1}

Sars and Ozone

Ozone is a naturally occurring energy-rich molecule embodying unique physico-chemical and biological properties suggesting a possible role in the therapy of SARS, either as a monotherapy or, more realistically, as an adjunct to standard treatment regimens.

Owing to the excess energy contained within the O [sub]3 molecule, it is theoretically likely that O [sub]3 , unlike organism-specific antiviral options available today, will show effectiveness across the entire genotype and subtype spectrum of SARS. [sup][25]

Mechanism of Action

Inactivation of bacteria, viruses, fungi, yeast and protozoa: Ozone therapy disrupts the integrity of the bacterial cell envelope through oxidation of the phospholipids and lipoproteins. In fungi, O [sub]3 inhibits cell growth at certain stages. With viruses, the O [sub]3 damages the viral capsid and upsets the reproductive cycle by disrupting the virus-to-cell contact with peroxidation. The weak enzyme coatings on cells which make them vulnerable to invasion by viruses make them susceptible to oxidation and elimination from the body, which then replaces them with healthy cells. [sup][26]

Stimulation of oxygen metabolism: Ozone therapy causes an increase in the red blood cell glycolysis rate. This leads to the stimulation of 2,3-diphosphoglycerate which leads to an increase in the amount of oxygen released to the tissues. Ozone activates the Krebs cycle by enhancing oxidative carboxylation of pyruvate, stimulating production of ATP. It also causes a significant reduction in NADH and helps to oxidize cytochrome C. There is a stimulation of production of enzymes which act as free radical scavengers and cell-wall protectors: glutathione peroxidase, catalase and superoxide dismutase. Production of prostacyline, a vasodilator, is also induced by O [sub]3 [Figure 1]. [sup][25] {Figure 1}

Activation of the immune system: Ozone administered at a concentration of between 30 and 55 [micro]g/cc causes the greatest increase in the production of interferon and the greatest output of tumor necrosis factor and interleukin-2. The production of interleukin-2 launches an entire cascade of subsequent immunological reactions. [sup][27]

Mechanism of action of O [sub]3 on the human lung: Ozone exposure induces a significant mean decrement in vital capacity. It significantly increases mean airway resistance and specific airway resistance but does not change dynamic or static pulmonary compliance or viscous or elastic work. It also significantly reduces maximal transpulmonary pressure. And further more significantly increases respiratory rate and decreased tidal volume. [sup][27]

Clinical Trials

The study to evaluate effect of bimosiamose on O [sub]3 -induced sputum neutrophilia: Biomosiamose is an anti-inflammatory glycomimetic and selectin inhibitor. [sup][28] It is found effective against disease states involving inflammatory cells like for example for asthma. [sup][29] This drug, as per last updation, was in phase 2 trials and being evaluated for its efficacy and safety in treating chronic pulmonary obstructive disease (COPD), the study is sponsored by Revotar Biopharmaceuticals AG and was carried out by NCT00962481 (ClinicalTrials.gov Identifier). [sup][30]

Evaluate the effects of the drug (SB-656933-AAA) on the body after a single dose in subjects who have inhaled O [sub]3 : Drug SB-656933-AAA was developed by GlaxoSmithKline which was found to exhibit good activity in treating COPD as well as cystic fibrosis. This action was found to be enhanced by administration of a single dose of O [sub]3 before administration of the aforementioned drug. This drug until latest updated data was in phase 1 stage, study was carried out by NCT00551811. [sup][31]

Intraarticular O [sub]3 therapy for pain control in osteoarthritis of the knee: Ozone is being currently tested for its effectiveness in relieving the pain in patients suffering from osteoarthritis of the knee. The current status of the study is phase 2 which is sponsored by Ben-Gurion University of the Negev and the study being conducted by NCT00832312. [sup][32]

The Effect of Ozone Therapy for Lumbar-Herniated Disc: Ozone is also being evaluated for its efficacy infiltration and its effectiveness in comparison with microdiscectomy in the treatment of lumbar-herniated disc with criteria for surgery. The study is currently in its phase 2 studies, which is sponsored by Kovacs Foundation and trials being carried out by NCT00566007. The study also evaluates the efficacy of infiltration in presence of corticoids, anesthetics, which is being compared by replacing O [sub]3 by oxygen. [sup][33],[34],[35]

Advantages of Ozone Therapy

Diabetic complications are attributed to the oxidative stress in the body, O [sub]3 was found to activate the antioxidant system affecting the level of glycemia. Ozone prevented oxidative stress by normalizing the organic peroxide levels by activating superoxide dismutase. [sup][36],[37] Ozone was found to completely inactivate the HIV in vitro , this action of O [sub]3 was dose-dependent. Concentration used for inactivation was found to be non-cytotoxic. The inactivation was owing to the reduction of the HIV p24 core protein. [sup][38] Ozone was also found to increase the host immunity by increasing the production of cytokine. [sup][39] In an in vitro study, it was observed that O [sub]3 is very effective in reducing the concentrations of Acinetobacter baumannii , Clostridium difficile and methicillin-resistant Staphylococcus aureus in dry as well as wet samples, hence it can be used as a disinfectant. Oxygen/ O [sub]3 mixture was also found to prolong the appearance of arrhythmia induced by potassium chloride, aconitine, etc., in laboratory animals like rats. [sup][40]

Disadvantages of Ozone Therapy

An array of ill-effects are observed owing to the reactivity of O [sub]3 viz oxidation, peroxidation or generation of free radicals and giving rise to cascade of reactions like peroxidation of lipids leading to changes in membrane permeability, [sup][41] lipid ozonation products (LOP) act as signal transducer molecules. [sup][42] The main reason for this being presence of unsaturated fatty acids in both lung lining fluid and pulmonary cell bilayers, O [sub]3 reacts with unsaturated fatty acids to give their specific products i.e., LOP, which activates the lipases triggering the release of endogenous mediators of inflammation. [sup][43] The loss of functional groups in enzymes leading to enzyme inactivation. These reactions further results in cell injury or eventual cell death. Combinations of O [sub]3 and NO [sub]2 occur in photochemical smog, have hazardous effects on lung alveoli and act additively or synergistically. Dietary antioxidants or free radical scavengers like vitamin E, C, etc., can prevent aforementioned effects of O [sub]3 . [sup][44],[45]

In an in vitro study it was observed that arachidonic acid was oxidized in presence to O [sub]3 to give peroxides, viz. arachidonic acid peroxides (AAP), having activity comparable to prostaglandin endoperoxides. These peroxides were fond to show following actions contraction of rabbit aortic strips and rat fundus strips in presence on indomethacin and Vane's mixture of vasoactive hormones at doses comparable to naturally formed prostaglandin peroxides. AAP also caused aggregation of human platelets in platelet-rich plasma, but these effects were not observed in presence of indomethacin and vitamin E, which indicated that these can be used to treat such toxicity of O [sub]3 . [sup][46]

Recent Development

Ozone was effectively used as an antibacterial agent to treat oral infections caused by Actinomyces naeslundii, Lactobacilli casei and Streptococcus mutans. Exposure of about 60 s exhibited 99.9% killing efficiency, but exposure for such a long period showed degradation of saliva proteins. So exposure of 10 s to 30 s was proved effective to kill significant number of bacteria. [sup][47]

A single subcutaneous injection of O [sub]3 in mouse with spared nerve injury of the sciatic nerve was found to decrease the neuropathic pain-type behavior. Mechanism of this action is yet unclear but O [sub]3 was observed to regulate the expression of the genes that play vital role in onset and maintenance of allodynia. [sup][48]

Acknowlegdement

The authors would like to thank Mr. Deepak Ahire, Ex-lecturer of Pharmaceutical Chemistry, V.E.S. College of Pharmacy, for enlightening us with some key points on Ozone Therapy and for successful completion of the article.

References

1. Di Paolo N, Bocci V, Gaggioti E. Ozone therapy editorial review. Int J Artificial Organs 2004;27:168-75.

2. Bocci V. Biological and clinical effects of ozone: Has ozone therapy a future in medicine? Br J Biomed Sci 1999;56:270-9.

3. Bocci V. Does ozone therapy normalize the cellular redox balance? Implications for the therapy of human immunodeficiency virus infection and several other diseases. Med Hypothesis 1996;46:150-4.

4. Razumovskii, Zaikov. Ozone and its reactions with organic compounds. New York: Elsevier; 1984. Available from: http://ozonicsint.com/articles_vivo.html.

5. Health and Environmental Effects of Ground-Level Ozone. U.S. EPA, July 1997. Available from: http://www.practicalasthma.net/pages/topics/aaozone.htm.

6. Folinsbee LJ. Effects of ozone exposure on lung function in man. Rev Environ Health 1981;3:211-40.

7. Bocci V. Is it true that ozone is always toxic? The end of a dogma. Toxicol Appl Pharmacol 2006;16:493-504.

8. Holmes J. Clinical reversal of root caries using ozone, double-blind, randomised, controlled 18-month trial. Gerodontology 2003; 20:106- 14.

9. Hernandez F, Menendez S, Wong R. Decrease of blood cholesterol and stimulation of antioxidative response in cardiopathy patients treated with endovenous ozone therapy. Free Radical Biol Med 1995;19:115-9.

10. Clavo B, Perez JL, Lopez L, Suarez G, Lloret M, Rodriguez V, et al . Effect of ozone therapy on muscle oxygenation. J Altern Complement Med 2003;9:251-6.

11. Shoemaker JM. Ozone therapy: History, physiology, indications, results. Available from: http://www.fullcircleequine.com/oz_therapy.pdf. [cited in 2010].

12. McLean L. The miracle of ozone therapy. Available from: http://www.zeusinfoservice.com/Articles/TheMiracleofOzoneTherapy.pdf. [cited in 2009 Jun].

13. Stoker G. Ozone in chronic middle ear deafness. Lancet 1902; 160:1187-8.

14. Wells KH, Latino J, Gavalchin J, Poiesz BJ. Inactivation of human immunodeficiency virus type 1 by ozone in vitro . Blood 1991; 78:1882- 90.

15. Carpendale MT, Freeberg JK. Ozone inactivates HIV at noncytotoxic concentrations. Antiviral Res 1991;16:281-92.

16. Haug KF, Heidelberg, Rilling S, Viebahn R. The use of Ozone in Medicine, classical medical ozone textbook, 11 edition, 1987.

17. Sunnen GV. Ozone in medicine: Overview and future directions. J Adv Med 1988;1:159-74.

18. Washutti J, Viebahn R, Steiner I. The influence of ozone on tumor tissue in comparison with healthy tissue. Ozone Sci Engg 1990;12:65- 72.

19. Washutti J, Viebahn R, Steiner I. Immunological examinations in patients with chronic conditions under administration of

ozone/oxygen mixtures. Ozone Sci Engg 1989;11:411-7.

20. Zanker KS, Kroczek R. In vitro synergistic activity of 5-fluorouracil with low-dose ozone against a chemoresistant tumor cell line and fresh human tumor cells. Int J Exp Clin Chemother 1990;36:147-54.

21. Bocci V, Paulesu L. Studies on the biological effects of ozone 1: Induction of interferon on human leucocytes. Haematologica 1990;75:510-15.

22. Viebahn-Hansler R . Ozone therapy-the underlying therapeutical concept and models of efficacy. Erfahrungs Heilkunde vol 4, 1991. p. 40.

23. Kawalski H, Sondej J, Cierpiol TE. The use of ozonotherapy in nose correction operations. Acta Chirurgiae Plasticae 1992; 34:182-4.

24. Johnson AS, Ferrara JJ, Steinberg SM. Irrigation of the abdominal cavity in the treatment of experimentally induced microbial peritonitis: efficacy of ozonated saline. Am Surg J 1993;59:297-303.

25. Gerard V, Sunnen MD. SARS and ozone therapy: Theoretical considerations. Available from: http://www.triroc.com/sunnen/topics/sars.html. [cited in 2003].

26. Why consider ozone therapy/oxygen Spa as alternative treatment dallas fort worth? Available from: http://www.holisticbodyworker.com/ozone_therapy_documentation.html. [cited in 2010].

27. Viebahn-Hansler R. The use of ozone in medicine: Mechanisms of action. Munich May 23-25, 2003. Available from: http://www.oxidation-therapy.com/pdfs/MechanismofAction.pdf.[cited in 2003].

28. Bimosiamose: An Antiinﬂammatory Glycomimetic. available from: http:// www.revotar.de/pdf/BioTOPics24_Bock.pdf. [cited in 2010].

29. Beeh KM, Beier J, Meyer M, Buhl R, Zahlten R, Wolff G. Bimosiamose, an inhaled small-molecule pan-selectin antagonist, attenuates late asthmatic reactions following allergen challenge in mild asthmatics: a randomized, double-blind, placebo-controlled clinical cross-over-trial. Pulm Pharmacol Ther 2006;19:233-41.

30. Study to evaluate the effect of bimosiamose on ozone induced sputum neutrophilia. Available from: http://clinicaltrials.gov/ct2/show/NCT00962481. [cited in 2010].

31. Evaluate the effects of the drug (SB-656933-AAA) on the body after a single dose in subjects who have inhaled ozone. Available from: http://clinicaltrials.gov/ct2/show/study/NCT00551811. [cited in 2010].

32. Intraarticular ozone therapy for pain control in osteoarthritis of the knee. Available from: http://clinicaltrials.gov/ct2/show/NCT00832312?term=ozone+therapyandrank=2 . [cited in 2010].

33. The Effect of Ozone Therapy for Lumbar Herniated Disc. Available on: http://clinicaltrials.gov/ct2/show/NCT00566007?term=ozone+therapyandrank=1. [cited in 2010].

34. Andreula CF, Simonetti L, De Santis F, Agati R, Ricci R, Leonardi M. Minimally invasive oxygen-ozone therapy for lumbar disk herniation. AJNR Am J Neuroradiol 2003;24:996-1000.

35. D'Erme M, Scarchilli A, Artale AM. Ozone therapy in lumbar sciatic pain. Radiol Med 1998;95:21-4.

36. Hazucha MJ, Bates DV, Bromberg PA. Mechanism of action of ozone on the human lung. J Appl Physiol 1989;67:1535-41.

37. Martinez-Sanchez G, Al-Dalain SM, Menendez S, Re L, Giuliani A, Candelario-Jalil E, et al . Therapeutic efficacy of ozone in patients with diabetic foot. Eur J Pharmacol 2005;523:151-61.

38. Carpendale MT, Freeberg JK. Ozone inactivates HIV at noncytotoxic concentrations. Anitiviral Res 1991;16:281-92.

39. Bocci V. Ozonization of blood for the therapy of viral diseases and immunodeficiencies: A hypothesis. Med Hypothesis 1992; 39:30-4.

40. Sharma M, Hudson JB. Ozone gas is an effective and practical antibacterial agent. Am J Infect Control 2008;36:559-63.

41. Di Filippo C, Cervone C, Rossi C, di Ronza C, Marfella R, Capodanno P, et al . Antiarrhythmic effect of acute oxygen-ozone administration to rats. Eur J Pharmacol 2010;629:89-95.

42. Pryor WA, Squadrito GL, Friedman M. A new mechanism for the toxicity of ozone. Toxicol Lett 1995;82-83:287-93.

43. Pryor WA, Squadrito GL, Friedman M. The cascade mechanism to explain ozone toxicity: The role of lipid ozonation products. Free Radical Biol Med 1995;19:935-41.

44. Donovan DH, Williams SJ, Charles JM, Menzel DB. Ozone toxicity: Effect of dietary vitamin E and polyunsaturated fatty acids. Toxicol Lett 1977;1:135-9.

45. Mustafa MG. Biochemical basis of ozone toxicity. Free Radical Biol Med 1990;9:245-65.

46. Roycroft JH, Gunter WB, Menzel DB. Ozone toxicity: Hormone-like oxidation products from arachidonic acid by ozone-catalyzed autoxidation. Toxicol Lett 1977;1:75-82.

47. Johansson E, Claesson R, van Dijken JW. Antibacterial effect of ozone on cariogenic bacterial species. J Dent 2009;37:449-53.

48. Fuccio C, Luongo C, Capodanno P, Giordano C, Scafuro MA, Siniscalco D, et al . A single subcutaneous injection of ozone prevents allodynia and decreases the over-expression of pro-inflammatory caspases in the orbito-frontal cortex of neuropathic mice. Eur J Pharmacol 2008;603:42-9.

A. Elvis, J. Ekta