The case for oxygen-ozonetherapy

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ABSTRACT

Ozone is a very reactive gas that is toxic to the respiratory system. However, under controlled conditions, it can be therapeutically useful in several human diseases. An unfavourable combination of factors (ozone is one of the worst troposphere pollutants) and past misuse have led to misgivings about ozonetherapy. However, basic and clinical work developed over the past 10 years has clarified the fundamental mechanisms of action of ozone in biology and medicine. Interestingly, judicious doses of ozone dissolved in blood trigger a cascade of well-defined chemical compounds acting on multiple cellular targets according to well-known molecular, biochemical and pharmacological pathways. Ozonetherapy is proving to be very useful in age-related macular degeneration, ischaemic and infectious diseases, and in wound healing disorders, where conventional medicine has failed. Critical evaluation of the potential therapeutic utility of this simple, inexpensive medical application by national and international health authorities is warranted and may lead to clinical benefit for a large proportion of the world's population.

KEY WORDS: Communicable diseases.
Ischemia.
Lung diseases.
Macular degeneration.
Neoplasms.
Ozone.

Introduction

The title of this brief review intends to be constructively provocative because oxygen-ozonetherapy is often thought of as toxic, with scant evidence to justify its use in medicine. However, the author will demonstrate that these suppositions are incorrect.

There is no doubt that ozone, the third strongest oxidant in chemistry, is intrinsically toxic. The respiratory system[1] and, to a lesser extent, mucosal membranes and skin[2] should never be exposed to ozone and other pollutants because they enjoy little protection from the antioxidants present in the aqueous-lipid film layer.

During summer months, the bronchial–alveolar lining, which is exposed daily to air polluted with 90–100 ppb ozone, produces toxic compounds (e.g., reactive oxygen species [ROS], lipid oxidation products [LOPs], proinflammatory cytokines and proteases) that damage the lungs and, after being absorbed by lymphatics and capillaries into the circulation, vital organs.[3]

Moreover, saline-washed erythrocytes suspended in saline[4] or cells in culture[5] undergo haemolysis or apoptosis. respectively, even if exposed to very low ozone concentrations, as they fail to be protected by natural antioxidants such as ascorbate, uric acid, albumin and α-tocoferol.[6,7] However, these experimental data are misleading because, while human blood is endowed with a potent antioxidant system,[6,7] washed erythrocytes or cells cultured in antioxidant-poor media[8] are very sensitive to ozonation. This has persuaded chemists and cell biologists to establish the dogma that ozone is cytotoxic and should not be used in medicine.

In the 1990s, the direct intravenous (iv) administration of oxygen-ozone in human immunodeficiency virus (HIV)-infected patients, in the belief that ozone would destroy the virus, often resulted in pulmonary embolism. This resulted in the prohibition of ozonetherapy in several states in the USA. In addition, incorrect use of ozonetherapy has further contributed to the defamation of ozonetherapy.

In a recent review,[9] ozone is compared to the Roman god Janus because it has opposing effects: it is toxic in the troposphere[3] or if generated during inflammation,[10] but it is very useful in the stratosphere, where it blocks ultraviolet (UV) rays and is now used widely for water sterilisation,[11] food processing[11] and in veterinary medicine.[12] Moreover, when ozone is used as a drug in a well-defined therapeutic window, its oxidant activity is quenched by the antioxidant system (enzymes and hydrophilic and lypophilic compounds) present in blood and tissue.[6,7]

It is widely appreciated that any chemical compound, depending on its dosage, can be beneficial or toxic. The most striking example is glucose, which, while essential for life at physiological concentration, can be lethal if it falls below 0.4 mg/mL or is constantly higher than 1.3 mg/mL. Thus, although intrinsic toxicity of ozone must be borne in mind, only a few deaths and side effects have been recorded.[13] In contrast, Vioxx may have caused the death of as many as 55,000 people during the past four years in the USA.[14]

Update of clinical results

Since 1988 the author and colleagues have investigated the therapeutic potential of ozone scientifically using precise ozone generators, which allows continual checking of the ozone concentration in real time by a photometer calibrated using the classical iodometric method. Some reviews[9,15,16] and two critical books[12,17] have reported the first comprehensive

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framework for understanding and recommending ozonetherapy in some diseases.

Today, ozone is considered to be a drug and thus it must be used with caution after carefully defining its therapeutic window[9,16] (from 10 μg/mL [0.21 μmol/mL] up to 80 μg/mL [1.68 μmol/mL] blood). Thus, it is important to calibrate precisely the ozone dose used against the antioxidant capacity of the patient's blood, thereby limiting potential ozone toxicity.

Clinical applications demonstrate that the classical treatment, denominated ozonated autohaemotherapy (O_3-AHT), which consists of exposing a precise volume of blood to a precisely calibrated ozone dose for a few minutes, followed by re-infusion of activated blood to the donor, stimulates several biochemical pathways[15,16] without producing acute or chronic toxicity.[18] The potent antioxidant capacity of blood tames the reactivity of a calculated ozone dose and readily reconstitutes the antioxidant titre.[19,20]

In addition, the concept that ozone is always toxic is inconsistent with the knowledge that another two potentially toxic gaseous molecules (nitric oxide [NO] and carbon monoxide [CO]) can operate as crucial cell activators after short exposure to low concentrations in particular cells and tissues.[3] On the other hand, during chronic inflammation typical of viral and autoimmune disease, diabetes, atherosclerosis and cancer, excessive and constant release of ROS, NO and peroxynitrite are detrimental and perpetuate the pathological state. Thus, it is possible that precise and brief (2–3 min) oxidative stress induced by 'physiological' ozone concentrations cannot be equated to the pathological chronic oxidative stress caused by excessive and constant release of ROS unchecked by antioxidants.

Contrary to expectations, the judicious application of ozone in infectious disease,[15–17,21] the atrophic form of age-related macular degeneration (ARMD),[17] vasculopathies,[22–31] diabetes,[32] wound healing disorders,[17,21] orthopaedics[33] and dentistry[34,35] has yielded striking results. Therefore, it would seem appropriate to reconsider the potential of ozone in other diseases.

As soon as it is dissolved in the aqueous part of plasma, ozone reacts immediately with antioxidants and polyunsaturated fatty acids, generating a cascade of well-defined compounds such as hydrogen peroxide and lipid peroxidation products, in particular 4-hydroxynonenal,[36] that are able to activate blood, endothelial and parenchymal cells responsible for biological and therapeutic responses in various diseases.

The versatility of ozone is due to the generation of chemical compounds, some of which have disinfectant activity, while others, acting on cells with different functions, exert a number of biological responses. This explains why ozonetherapy, in combination with conventional medicine, can be applied only in specific diseases and should not be seen as a panacea for all ills. In reality, it may be specifically useful in only a few pathologies where orthodox medicine has proved inadequate. The following examples aim to clarify this concept.

Age-related macular degeneration

In the UK alone, some 200,000 patients affected by the dry form of ARMD are suitable for treatment with O_3-AHT.[37] Nonetheless, ophthalmologists can only prescribe antioxidants and zinc, which are only modestly effective.[38] Since 1995, almost 700 patients with the dry form of ARMD have been treated with O_3-AHT and three-quarters have shown an improvement of one to two lines on the visual acuity chart.[16,17]

Usually 15-18 treatments, at an initial ozone concentration of 20 μg/m of gas per mL blood, slowly upgraded to 40 μg/mL (twice weekly), followed by a monthly session as a maintenance therapy, permit continued visual acuity.[17] Although uncontrolled, this study emphasises that ozone therapy can improve the patient's quality of life dramatically.

In this disease there is progressive degeneration and death of the fovea centralis photoreceptors and of the pigmented retinal epithelium (PRE) as a consequence of several factors, one of which is chronic hypoxia. Although ozonetherapy induces a pleiotropic response, the main advantage is increased delivery of oxygen to the retina.

It is worth noting that ozonetherapy is useless, even harmful, in the exudative form of ARMD and in multigenic and progressive disorders (e.g., retinitis pigmentosa and recessive Stargardt's disease).[17] The exudative form, characterised by an aberrant choroidal vascular growth and a vascular hyperpermeability beneath the retina and the PRE, is treated with several experimental therapies, such as photodynamic therapy with verteporfin or with the periocular or intravitreal administration of angiostatic inhibitors.[39–41]

It should be emphasised that orthodox therapies (in the exudative form) and ozonetherapy (in the dry form) not only improve visual acuity but also quality of life.

Vascular disease

Ozonetherapy, in comparison to pentoxyfylline and prostanoids (the gold standard of orthodox treatment), has proved more effective and less toxic in ischaemic vascular disease. In a small trial,[31] 28 patients were randomised to either receipt of their own ozonated blood or to iv infusion of prostacyclin. All patients continued conventional treatment with statins and antihypertensive and anti-platelet aggregation drugs. Ozonetherapy proved more effective than prostacyclin in terms of pain reduction and improvement in the quality of life, but no significant difference was seen in vascularisation of the lower limbs in either group, possibly due to the short duration of treatment (14 treatments in seven weeks).

Since 1982, several studies[22–30] have confirmed the validity of ozonetherapy in this complex pathology, but it is a mistake to stop therapy too early in these patients because ozonetherapy, as with other conventional drugs, must be continued for life. An improved schedule, as yet to be fully evaluated, consists of two-ozonated HAT (225 mL blood plus 25 mL 3.8% sodium citrate solution), given weekly for at least four months, with topical therapy with ozonated olive oil, is useful when initial dry gangrene or ulcers are present.

Millions of people suffer from chronic limb, brain and heart ischaemia, which represent the major cause of death worldwide. This has a huge socio-economic impact, particularly in the developing world. Despite the present lack of a proof of concept study in this patient group, it is

possible that ozonetherapy as an adjunct to conventional treatment may prove effective.

Metastatic cancer

Although cancer cells up-regulate glycolysis, even in aerobic conditions,[42] they thrive in hypoxia. The greater the hypoxia in the neoplastic environment, the more clinically aggressive is the cancer. It is now well known that hypoxia favours metastasis, and thus administration of anti-angiogenic proteins or anti-vascular endothelial growth factor (VEGF) antibodies should halt tumour growth. However, after massive investments in time and of money and energy, this approach has been disappointing. For example, survival of colon cancer patients treated with chemotherapy and bevacizumab was prolonged for just five months.[43] From a physiological perspective, it would seem logical to restore normoxia in the neoplastic environment.[44,45]

Preliminary study on a small number of preterminal patients has been performed, consisting of two ozonated-HATs and two minor AHTs (via intramuscular administration) weekly for at least six months. At the very least, improvement in oxygen transport and delivery should enhance the effect of radiotherapy and chemotherapy.[46,47] Furthermore, ozonetherapy exerts an anti-immunosuppressive effect and reduces the symptoms of fatigue, which plague almost 90% of patients.[48]

As soon as chemoresistance becomes evident, chemotherapy should be stopped and replaced by ozonetherapy, which, in the author's experience, improves the quality of life due to a feeling of wellness and euphoria.[16,17] If chemotherapy is continued, the patient becomes totally disabled, with a Karnofsky status below 40%. At this point even ozonetherapy is essentially useless.[17]

Diabetes mellitus

A controlled and randomised clinical trial was performed recently at the Institute of Angiology and Vascular Surgery, University of Havana, Cuba, in which 101 patients with diabetic foot were recruited. Fifty-two patients were treated 15 times in 20 days with ozone (local and rectal insufflation of the gas mixture, including about 96% oxygen and about 4% ozone, with a fixed ozone dose of 10 mg). Forty-nine patients were treated with systemic antibiotics and conventional topical treatment. The efficacy of these interventions was evaluated in both groups after 20 days of treatment.

Ozonetherapy improved glycaemic control, prevented oxidative stress, normalised levels of organic peroxides, increased intra-erythrocyte superoxide dismutase, enhanced ulcer healing and significantly reduced amputation rate. The authors[32] concluded that medical ozone treatment could be an alternative therapy in the treatment of diabetes and its complications. The Cuban study reports exceptional data that should be replicated in a much large controlled study as soon as possible. If rectal administration of ozone, which is an imprecise and biochemically less-effective procedure than O_3-AHT,[49] produces such exceptional improvements in advanced diabetes, then health authorities worldwide should evaluate the enormous potential of this therapy.

Lung disease

Lung diseases, such as chronic obstructive pulmonary disease (COPD), will soon become the fourth most common cause of death, which, with emphysema and asthma, cause significant incapacity. Using corticosteroids, long-acting β2-agonists and antibiotics, orthodox medicine has certainly proved helpful,[50] but it cannot change the course of COPD. However, in a series of elderly patients affected by macular degeneration and either emphysema or COPD, a remarkable improvement has been observed by combining ozonetherapy[17] (using the schedule adopted for vasculopathies) with the best conventional treatments.

Ozonetherapy also appears to be effective in asthma. Hernandez *et al*.[51] have treated 113 patients with three cycles during one year of either 15 ozonated AHT (applied at doses of 4 mg and 8 mg) or rectal insufflation of gas. In Cuba ozonetherapy is used in all hospitals and rectal administration has proved to be both practical and quick, although some patients have refused rectal administration of gas.

Using a fixed ozone concentration of 40 μg/mL per mL blood (8 mg dose) and after completion of the last cycle of 15 treatments, a significant reduction in IgE and HLA-DR levels was observed, together with increased blood antioxidant capacity, as determined by increased GSH and GSH peroxidase levels. They also noted a significant improvement in lung function and symptoms. On the other hand, rectal insufflation of gas (10 mg for each treatment per 20 sessions) in one group of patients was found less effective, indicating that ozonated AHT was the most effective treatment. The comparison of ozonetherapy with conventional therapies with respect to improvements in lung function are awaited.

Chronic infectious disease

Clearly, ozone is regarded as the best topical disinfectant because bacteria, viruses, fungi and protozoa, when free in water, are readily oxidised.[11,52–54] However, destruction of free pathogens in plasma by ozone, *ex vivo*, is hampered by soluble antioxidants such as albumin, ascorbic acid and uric acid, and they are virtually unassailable when intracellular.[55]

However, ozonetherapy still deserves attention because, by improving metabolism and operating as a mild cytokine inducer,[56–58] it can have a beneficial influence on infectious diseases. Thus, there remains a place for the application of ozonetherapy as an adjuvant in chronic viral infections (e.g., HIV), in combination with highly active anti-retroviral therapy (HAART), pegylated interferon-α plus either lamivudine or ribavirin and the acyclovirs.

Bacterial septicaemia must be treated with the most suitable antibiotics to prevent toxaemia and multisystem organ dysfunction. However, it should be kept in mind that ozone generates in blood the same ROS produced by granulocytes and macrophages during infection,[59] and this is one of the reasons for the efficacy of ozonetherapy. Particularly important is the topical application of ozone as a gas mixture (about 4% ozone and 96% oxygen), as ozonated water or ozonated olive oil (where ozone is stabilised as a triozonide)[60] for the treatment of, for example, bacterial, viral

and fungal infections, burns, abscesses and osteomyelitis.

Topical therapy is most effective when combined with O_3-AHT owing to oxygenation of hypoxic tissues. Radiodermititis[61] and wound healing have been enhanced because ozonated solutions display a cleansing effect, act as a disinfectant and stimulate tissue reconstruction.

In 1996, 6.5 million people in the USA suffered from diabetic ulcers, at an annual cost of about $21 billion.[62] As previously discussed,[32] it is now possible to improve the prognosis of diabetes by combining ozonated topical therapy with the simple, inexpensive and risk-free rectal insufflation of oxygen-ozone, which could be carried out by the patient at home under the supervision of a physician.

Chronic ulcers and/or putrid wounds are one of the most distressing and difficult medical problems with which to deal, and are caused by ischaemia, diabetes, immunosuppression and malnutrition. During the past decade the use of ozone in such cases has proved very beneficial.[12,17] With the current increase in medical costs, ozonetherapy deserves attention because it reduces hospital assistance and is cheap.

Another exciting finding is that ozone, when properly used with O_3-AHT, can up-regulate the intracellular synthesis of antioxidant enzymes and the most protective stress protein, haem oxygenase-1.[16,63] Thus, ozone can induce an adaptive response and is the only drug able to correct the chronic oxidative stress observed in cancer, diabetes, uraemia, atherosclerosis, chronic infection and neurodegenerative diseases. Small ozone doses induce stimulation, while high ones cause inhibition.[64]

In comparison with the inconclusive usefulness of oral antioxidants, experimental and clinical data[32,65–70] show that the cautious and prolonged use of ozonetherapy can arrest or delay the progression of these diseases and improve the quality of life. However, some patients respond less well to repeated and minimal oxidative stress, which may be due to an advanced stage of disease or to polymorphism of the Ncfl protein, which is an essential component of the NADPH oxidase complex.[71] Interestingly, Hultqvist *et al*.[72] suggest the use of phytol to overcome the effect of possible genetic mutations in patients with rheumatoid arthritis.

Dentistry and orthopaedics

Recently, ozone has proved very useful in dentistry for eliminating infection and blocking primary root carious lesions.[34,35]

The application of ozone in low back pain has proved very effective. It can be administered directly (intradiscal)[33,73] or indirectly[17] via intramuscular administration into the paravertebral muscles. Ozone exerts a multiplicity of effects, such as the activation of the anti-nociceptive system, and has anti-inflammatory action due to lipid peroxidation products, with the consequent inhibition of cyclooxygenase-2.[74,75]

Conclusions

Ozonetherapy is well known among complementary medical approaches, but is yet to be practised correctly in many situations. However, on the basis of basic and small clinical studies performed over the past decade, it has become clear that ozone, in judicious dosages, behaves as a drug and that its biochemical and pharmacological mechanisms of action are in the realm of orthodox medicine.

Ozone is an extremely versatile drug and the therapeutic range has been defined precisely to exclude acute and chronic toxicity. The majority of patients report a feeling of wellbeing during prolonged ozone therapy.

In chronic cutaneous infection, which affects millions of patients, the use of parenteral and topical application of ozone is far more effective than conventional medication in enhancing healing, simply because ozone disinfects, oxygenates and stimulates cell proliferation.

Clearly, there is evidence for the usefulness of ozonetherapy in the diseases outlined above and now is the time for conventional multicentre clinical trials to be undertaken. Owing to the potential cost savings, it is hoped that national and international health authorities will undertake such studies in conjunction with national associations devoted to ozonetherapy.

A recent editorial[76] addressed the problem of the "catastrophic failures of public health". The author of this review believes that the implementation of ozonetherapy in all hospitals could be a first important step in the right direction.

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