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Oxygen Toxicity

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Abstract

Oxygen therapy is like a two-edged sword, at one edge oxygen is essential for human survival, while at the other edge it may become toxic at an elevated partial pressure. This is a hazard, especially in intensive care units, where oxygen therapy may be administered over a period of days. Oxygen toxicity usually manifests in one of several forms including central nervous system mainfestations, pulmonary manifestations, and ocular manifestations, especially in premature neonates. The major factors affecting the onset and the severity of the toxicity are the concentration of the gas used, the duration of the exposure, and the susceptibility of the individual person. Because the treatment is being purely symptomatic, prevention and early recognition of the toxicity is of prime importance.

Key words : Oxygen toxicity; Hyperbaric oxygen therapy (HBOT); Free radicals.

Introduction

Oxygen is the second most common gas forming the normal external air (20.93 percent), preceded only by nitrogen (78.10 percent). Oxygen is vital to sustain life. The parital pressure of oxygen, in inspired air, at sea level is about 160 mm Hg.

Priestley, who discovered the oxygen, was himself amongst the first to suggest that there may be adverse affects of this 'pure air', when in 1775, he observed a candle to burn out faster in oxygen than in air, and wondered if 'the animal powers too be soon exhausted in this pure kind of air'[1].

The CNS effects of oxygen toxicity are called 'Bert effect' named after Paul Bert, who, in 1878, demostrated convulsions in larks exposed to 15-20 ATA (atmosphere absolute air)[2]. The so called 'Smith effect' is the pulmonary effects of oxygen toxicity, named after J Lorain Smith, who, in 1899, while trying to reproduce 'Bert effect', noticed fatal pneumonia in rats after 4 days of exposure to 73% oxygen at 1 ATA[1,2].

The clinical settings in which oxygen toxicity occurs are broadly divided into two groups; one is in which the patient is exposed to very high concentrations of oxygen for short duration, like in HBOT, and the second is in which lower concentrations of the gas are used but for longer duration. These two can result in the so called 'acute' and 'chronic' oxygen toxictiy, respectively. The acute toxicity has predominant CNS effects, while chronic toxicity has predominant pulmonary effects[1,3,4].

Hyperbaric oxygen therapy (HBOT)

Hyperbaric oxygen is oxygen administered at higher than atmospheric pressure. It is commonly used in carbon monoxide poisoning, decompression sickness, respiratory distress of newborn, anaerobic infections, e.g., gas gangrene caused by *Cl. welchi*, refractory chronic osteomyelitis with draining lesions, infected superficial burns, and to sensitise the tumour to radiotherapy. If HBOT is used for longer duration, sometimes even for short duration, it can lead to oxygen toxicity[5].

Classification and clinical manifestations of oxygen toxicity

(A) Central nervous system toxicity – 'Bert effect'

Though Bert originally described that CNS toxicity occured at oxygen pressures of > 3 ATA, it may however, occur at lower pressures if exposure is prolonged. Though early manifestations are variable, twitching of perioral and small muscles of the hand is a fairly constant feature[6]. Intense peripheral vasoconstriction due to hyperoxia and diaphragmatic

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twitching can result in facial pallor and 'cogwheel' breathing, respectively[4,7]. Continuation of exposure can lead to vertigo and nausea followed by altered behaviour, clumsiness, and finally convulsions. The convulsions are usually tonic-clonic, and the patient has no memory of the crisis[4,8]. A neurogenic pulmonary oedema concomitant with the convulsions has also been reported[9]. The factors aggravating the CNS toxicity are raised pCO_2, stress, fatigue, cold, and dietary deficiency of trace elements such as selenium, zinc and magnesium[1,4,10]. CNS toxicity is mainly due to oxidation and polymerisation of -SH groups of enzymes leading to their inactivation, which in turn results in cellular damage.

(B) Pulmonary toxicity – 'Smith effect'

Pulmonary effects of oxygen toxicity can occur after a prolonged exposure to oxygen > 0.5 ATA. Symptoms appear after a latent period whose duration decreases with increase in pO_2. In normal humans, the first signs of toxicity appear after 10 hours of oxygen at 1 ATA[6].

Pathology and pathophysiology

Prolonged and/or high concentrations of oxygen may damage the pulmonary epithelium, and inactivate the surfactant, form intra-alveloar oedema and interstitial thickening, and later fibrosis, leading to pulmonary atelectasis[5,11]. The lung lesions resemble those of paraquat poisoning[12].

Clinical features

These can be divided into three phases :

(a) Tracheobronchitis,
(b) Acute respiratory distress syndrome (ARDS), and
(c) Pulmonany interstitial fibrosis[6].

100% oxygen can be tolerated at sea level for about 24-48 hours without any serious tissue damage. Longer exposures produce definite tissue injury. There is mild carinal irritation on deep inspiration after 3-6 hours of exposure of 2 ATA oxygen, intense carinal irritation with an uncontrolled coughing after 10 hours, and finally chest pain and dyspnoea can develop. In majority of patients, these symptoms subside 4 hours after cessation of exposure[13].

(C) Ocular effects

Reversible constriction of the peripheral field of vision, a progressive but reversible myopia, and delayed cataract formation can occur. Ocular effects may be more when the entire eye is itself exposed to high ambient oxygen concentration and pressure, as in an oxygen tent, rather than when hyperoxia occurs via arterial circulation, e.g., following oxygen administration via a facemask[4].

Retrolental fibroplasia

There is formation of an opaque membrane behind the lens. Retrolental fibroplasia is one of the largest single cause of blindness during childhood (usually within 6 months). The cause is almost always related to the liberal administration of high concentration of oxygen above 40% for a prolonged period (1-2 days) following birth. Premature infants of less than 30 weeks of gestation or 1,500 grams birth weight appear to be at a greater risk [14]. They are also likely to develop chronic lung disease and intraventricular haemorrhage due to oxygen toxicity.

Pathology of retrolental fibroplasia[15]

Normally, retinal vascularisation continues shortly after birth. Oxygen of high concentrations and/or prolonged duration induces vasoconstriction, especially to the temporal portion of the retina which is the last to be vascularised, and there is obliteration of the lumen due to anoxic endothelial damage. After withdrawal of oxygen therapy, regeneration of the vessels in the area occurs with extension into the vitreous beyond the retina. Dilatation and rupture of these vessels can lead to vitreous or retinal haemorrhage, fibrosis, and adhesions leading to retinal detachment and blindness.

(D) Toxic effects on other tissues

Abnormal RBC morphology with or wihtout a reduction in circulating mass of RBCs with occasional episodes of haemolysis following HBOT have been observed[1].

Serous otitis media and dysbaric osteonecrosis in astronauts have also been observed, which may be partially contributed to high oxygen concentrations during space flights[1].

(E) Carbon dioxide narcosis

In patients with chronic obstructive pulmonary disease (COPD), status asthmaticus, weakness of the respiratory muscles (e.g., from polyneuritis, poliomyelitis, or myasthenia gravis), and in those with central respiratory depression from narcotic poisoning, head injury, or raised intracranial tension, the alveolar ventilation is inadequate to prevent a rise in the arterial carbon dioxide tension ($PaCO_2$). With increasing hypercapnia (raised $PaCO_2$), the respiratory centre becomes progressively more tolerant of CO_2 and its activity is solely maintained by the stimulus of hypoxaemia (hypoxaemic drive) reflexly through carotid and aortic bodies. A removal of this stimulus by oxygen administration reduces this ventilation still further with a consequent rise in $PaCO_2$. This gives rise to the syndrome of carbon dioxide narcosis with raised intracranial tension; clinically manifesting by sweating, twitchings, drowsiness, convulsions, papilloedema, and coma. It is a potentially lethal condition[5].

Pathophysiology of oxygen toxicity

Oxygen derived free radicals had been suggested by Gerschman *et al* in 1954, as being the probable aetiological factor in the development of these toxic effects[9]. Free radicals are produced as a result of mitochondrial oxireductive processes and also produced by the action of enzymes such as xanthine/urate oxidase at extra-mitochondrial sites, from auto-oxidative reactions, and by phagocytes during bacterial killing. These free radicals cause lipid peroxidations, especially in the cell membranes, inhibit nucleic acids and protein synthesis, and inactivate cellular enzymes. Normally, various antioxidant enzymes, e.g., glutathione peroxidase, catalase, and superoxide dismutase protect the body from these free radicals, but in hyperoxic situations, there is explosive free radical production leading to swamping of the enzyme systems and as a result free radicals escape inactivation[6].

Oxygen toxicity can also be exerted by non-radical mediated injury by cellular metabolic alteration or by enzyme inhibition. Glutamic acid decarboxylase is one such enzyme inhibited in the CNS and reduced level of gamma amino butyric acid (GABA) are seen concomitantly with occurence of seizures[1,9].

Prevention and monitoring of oxygen toxicity

Because the treatment is being purely symptomatic, prevention and monitoring for early recognition of toxicity is of prime importance. It should be remembered that sudden stoppage of oxygen at the onset of toxicity, may at times aggravate the symptoms-the 'oxygen off effect'[4].

Reduction in the vital capacity of the patient is an indicator to monitor pulmonary toxicity. The maximum acceptable reduction is 10%[4,13]. Dynamic lung compliance and the diffusing capacity for carbon monoxide (DLCO) are also observed to be reduced. To predict pulmonary damage after prolonged oxygen therapy, Unit of pulmonary toxicity dosage (UPTD) is calculated. One minute of 100% oxygen at 1 atmosphere is taken to produce 1 UPTD. A UPTD of 1,425 will produce a 10% reduction in the vital capacity[1].

Electroencephalogram (EEG) is of no value in the monitoring of CNS toxicity[4].

Acquired tolerance to hyperoxic exposure by induction of antioxidant enzymes by exposure to non-lethal levels of hyperoxia and/or hypoxia has been tried successfully in animals and is in the process of evaluation in man[10].

Exogenous antioxidants especially vitamin E and C may be used prophylactically in high risk infants. The recommended dose of vitamin E is 100 mg/kg/day for 4-6 weeks[5]. Adrenalectomy, hypophysectomy, and the hypothyroid state are associated with reduced severity of the toxicity as is the use of alpha adrenergic blockers[4,10]. As dietary deficiency of trace elements is likely to worsen the toxictiy, its supplementation may be helpful in deficient states.

The practical implications of the oxygen toxicity are as follows[11,15]

1. In patients with chronic hypoxaemia (as in severe COPD), it is wiser to use a concentration of oxygen that will correct dangerously low PaO_2 levels. A PaO_2 of even 50-55 mm Hg is generally sufficient in these patients.
2. Positive end-expiratory pressure (PEEP) should be used during mechanical ventilation, if an inspired

oxygen concentration > 50% fails to relieve dangerous hypoxia. But, even in above circumstances, PEEP should not be used in patients with COPD.

3. In acute pulmonary problems with severe hypoxia, the oxygen concentration must be sufficient to allow an oxygen saturation of above 90%. If, inspite of the use of PEEP, oxygen concentrations of more than 60-70% are needed to produce a satisfactory rise in PaO_2, it is wiser to choose to mainatin a PaO_2 in the mild-to-moderate hypoxaemic range.
4. Life threatening hypoxia must always be relieved even if this requires the use of 100% oxygen for prolonged periods of time.
5. To prevent retrolental fibroplasia, it is advisable to avoid continuous oxygen therapy especially in the premature and low birth weight neonates in concentration beyond 40%, and to keep the PaO_2 below the critical level of 160 mm Hg.

Conclusion

Though oxygen theapy is helpful in many disorders, its injudicious use may lead to toxic effects usually involving the CNS, the lungs and the eyes. As the management of the toxicity is purely supportive, its prevention and monitoring for early recognition is of great importance.

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