Place of Iron Chelators Like Desferrioxamine and Deferasirox in Management of Hyperoxia-induced Lung Injury; A Systematic Review

Sarah Mousavi, Mojtaba Mojtabahdezadeh and Mohammad Abdollahi
Faculty of Pharmacy and Pharmaceutical Sciences Research Center,
Tehran University of Medical Sciences, Tehran, Iran

Abstract: Supraphysiological concentrations of oxygen (hyperoxia) is necessary for treatment or prevention of hypoxemic condition, but hyperoxia through activation of oxidative stress pathways and generation of reactive oxygen species directly or indirectly result in lung injury and dysfunction. Many mediators are involved in the pathways to hyperoxic cell death seeming that transition metal ions especially iron promote the generation of the very reactive free radicals which are damaging to cells. Thus concerning the role of iron, a systematic review was conducted by reviewing all papers found from searching keywords of iron, lung injury, oxidative stress or hyperoxia in bibliography databases. Due to different pathways involved in hyperoxia-induced lung injury, several classes of drugs have been tested for example antioxidants, dexamethasone, pentoxifylline, erythropoetin, lisofylline, sildenafile, N-acetyl cysteine, or prostaglandine but some of them were not only successful but caused significant adverse effects. Findings indicate that metal ions especially iron through catalyzing of most reactive free radicals has a key role in oxidative stress process and hyperoxic condition and thus limitation of iron for prevention of hyperoxia-induced injury seems reasonable. Iron chelation has been recently used for conditions without iron overload such as neurodegenerative, infectious, reperfusion injury, cardioprotection. There are some evidences about positive effects of desferrioxamine alone or in combination when tested in animal models of lung injury or in human but they are not convincing. Further studies are necessary to clarify the importance of intervention with desferrioxamine or new long acting oral agent deferasirox and their risk/benefit in hyperoxia-induced lung injury.

Key words: Systematic review, iron chelator, hyperoxia-induced lung injury, oxidative stress, desferrioxamine, deferasirox

INTRODUCTION

High concentration of oxygen is essential for patients with hypoxic respiratory failure in intensive care unit, but prolonged exposure to oxygen cause tissue damage and lead to acute and chronic lung injury. Hyperoxia through direct oxygen toxicity and accumulation of inflammatory mediators within the lungs result in a process that initiate by damaging to pulmonary epithelium and endothelium and finally lead to pulmonary interstitial fibrosis (Ansari et al., 2008; Vazin et al., 2005a, b). Proliferation of type II alveolar epithelial cells, destruction of type I alveolar epithelial cell and pulmonary vascular remodeling are examples of changes in hyperoxic condition. No level of oxygen is safe indefinitely; studies of normal individuals exposed experimentally to 100% oxygen at normal pressure have shown evidence of tracheobronchitis and changes in vital capacity, diffusing capacity and lung permeability (Beckett and Wang, 1988; Davis et al., 1983). Inadvertent exposure of patients with normal lungs to prolonged hyperoxia resulted in clinical findings compatible with oxygen toxicity mainly through oxidative stress. Addition of hyperoxia to mechanical ventilation especially with high tidal volume augmented lung injury (Quinn et al., 2002). Different underlying mechanisms are involved in this process whereas oxidative stress is the major one that damage major macromolecules within cells resulting in cell apoptosis or death (Abdollahi et al., 2004). Concerning the importance of oxygen therapy, different drug classes have been tested for treatment or prevention of hyperoxia-induced lung injury specially by authors' team (Kajbaf et al., 2007; Mahmoodpoor et al., 2010; Mojtabahdezadeh et al., 2008; Najafi et al., 2009; Salari et al., 2005a, b; Soltan-Sharifi et al., 2007; Vazin et al., 2005a, b).

Neutrophils and macrophages are two major sources of reactive oxygen and nitrogen species (ROS and RNS) in the lung. Two major enzyme systems NADPH oxidase (Babior et al., 2002; Chung-Wai et al., 2003) and nitric oxide synthases (Bogdan, 2001) are responsible for
production of ROS or RNS especially superoxide anion, hydrogen peroxide and hydroxyl radical (Abdollahi et al., 2000a, b). Iron as a metal has especial role in production of hydroxyl radical, which can be explained in terms of following reactions (Lloyd et al., 1997):

$$\text{Fe}^{2+} + \cdot \text{O}_2 \rightarrow \text{Fe}^{3+} + \cdot \text{O}_2$$

$$\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^- \quad \text{(Fenton reaction)}$$

$$\text{Fe} + \cdot \text{O}_2 + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{2+} + \text{OH}^- + \text{OH}^- \quad \text{(Haber-Weiss reaction)}$$

The overall reaction is called Haber-weiss reaction (Lloyd et al., 1997). Hydroxyl radical react at diffusion-limited rates with various biomolecules including lipids, proteins, DNA (Nelson and McCord, 1998) and lead to cell injury (Rezaie et al., 2007). So chelation of iron could be a critical event in preventing iron-mediated oxidative stress.

**MATERIALS AND METHODS**

In order to provide enough data about the subject, we did systematic search utilizing Pubmed, Scopus, Google scholar and Embase databases. The initial search terms were iron, lung injury, oxidative stress or hypoxia to provide data about the role of iron in hypoxia-induced lung injury. Then search was continued with hypoxia, lung injury and treatment as keywords without narrowing or limiting search elements to find the most relevant literatures about the subject. References from each article were also evaluated for relevancy of inclusion in the study. All papers were reviewed to omit irrelevant or duplicate papers. Then their data were extracted into tables and summarized.

**RESULTS**

As summarized in Table 1, different drug classes have been used for treatment of hypoxia-induced lung injury. Almost all of the studies were done in animal models, because of the limitation to simulate same clinical condition of high concentrations of oxygen (>95%) for long duration and problems for sampling and analyzing of lung tissue or even bronchoalveolar lavage fluid in human (Cross et al., 1994; Van der Vliet et al., 1999). Furthermore, due to different pathways involved in

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<td>Lee et al.</td>
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<td>erythropoietin (rhEPO)</td>
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<td>Obara et al. (1985)</td>
<td>Neonatal rats</td>
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<td>Chakraborti et al. (1999)</td>
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<td>Paine et al. (2003)</td>
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<td>Increase of survival by preservation of alveolar epithelial barrier function</td>
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**MPO:** i.e.: Intraperitoneal, s.c.: Subcutaneously, i.v.: Intravenous, p.o.: Per oral, U/ml: mcg: Microgram, ppm: Part per million, kg: Kilogram, h: Hour, d: Day; SOD: Superoxide dismutase, CAT: Catalase, MAPK: Mitogen-activated protein kinases, VEGF: Vascular endothelial growth factor.
hyperoxia-induced lung injury, each drug targeted a part of this system (Ahmad et al., 2006; Cienciewicki et al., 2008; Lee and Choi, 2003; Romashko et al., 2003; Sprong et al., 1991).

Prevention or declining of inflammatory responses and proinflammatory cytokine release such as interleukine 6 or tumor necrosis factor alpha and improvement in antioxidant defenses by increasing activity of antioxidant enzymes such as superoxide dismutase and catalase and also blockade of neutrophil influx are the major mechanisms found for prevention or treatment of oxidative-induced lung injury (Auten et al., 2001; Ballard et al., 2007; Chakraborti et al., 1999; Chang et al., 2003; Davis et al., 1993; George et al., 1999; Mikawa et al., 1995; Obara et al., 1985; Ozzy et al., 2005; Rehan et al., 2006; Walther et al., 1995).

Other drugs result in improvement of pulmonary angiogenesis, vessel growth, alveolarization and decreasing pathological lung injury (Kunig et al., 2005; Ladha et al., 2005; Lee et al., 2007; Ozzy et al., 2005). Pentoxifylline (Ter Horst et al., 2004), erythropoietin (Ozzy et al., 2005), isoflurane (George et al., 1999) and sildenafil (De Visser et al., 2009) are examples of drug that attenuate alveolar fibrin deposition and result in increased survival of animals.

On the other hand some of the drugs especially some commonly used such as N-acetyl cysteine (Langley and Kelly, 1993; Van Klaveren et al., 1997), dexamethasone (Ramsey et al., 2000; Town et al., 1993) or prostaglandins (Hageman et al., 1989) have not been successful in treatment of hyperoxia-induced lung injury but even lead to some adverse effects on epithelial lung cells.

Alteration of pathways that lead to cell apoptosis such as mitogen-activated protein kinases (MAPKs) is another way that prevent lung damage (Hageman et al., 1989; Matthew et al., 2003; Paine et al., 2003; Reynolds et al., 2010; Veness-Meehan et al., 2000; Zinova-Herkenrova et al., 2008).

**DISCUSSION**

**Iron as a new target**: Iron is uptaken into epithelial cells for sequestration within ferritin. Alveolar macrophages elevate ferritin production after exposure to iron. They possess cell surface receptors specific for both haptoglobin and hemopexin to facilitate their removal (Birgens et al., 1998; Van Snick et al., 1977). Divalent metal transporter 1 (DMT1), Natural resistance-associated macrophage (Nramp) 1,2, transferrin and lactoferrin pathways are involved in iron sequestration in macrophages (Cellier et al., 1995) but continuous exposure overwhelms the capacity of ferritin to sequester the metal and finally releases it (Fig. 1). Ferritin is composed of 24 subunits of heavy (21 KD) and light (19 KD) chains and can reserve up to 4500 atom of Fe⁺ ion. H subunit has ferroxidase activity converting ferric to ferrous forms to fight against oxidative stress. The ratio between H and L subunits differs in different tissue. Increased H-subunit is found in proliferating tissues (Emerit et al., 2001; Harrison and Arosio, 1996). Tumor Necrosis Factor-α and Interleukin-1 transcriptionally induce the H ferritin (Torti and Torti, 2002). Ferritin synthesis is regulated post transcriptionally via the interaction of an iron-regulatory protein (IRP 1 and 2) with Iron Responsive Element (IRE) (Eisenstein, 2000). IRP-1 is an iron-sulfur cluster protein that exists in two forms when iron is abundant. It exists as acytosolic aconitase and IRP-1 that lossess its affinity for IRE. The mRNA of ferritin is translated and ferritin synthesis is increased. In the absence of iron, apo IRP-1 put on IRE and the mRNAs of TRF are stabilized and the translation of mRNA of ferritin is suppressed (Papanikolaou and Pantopoulos, 2005; Thomson et al., 1999). IRP-2 protein is abundant in iron insufficiency, but it degrades rapidly in iron excess through targeting of unique 73 amino acid sequence (Lavaute et al., 2001). Nitric oxide and H₂O₂ activate the IRP-1 through signaling mechanisms and thus mobilize iron from the 4 Fe-4S cubane cluster (Pantopoulos and Hentz, 1998). Down regulation of IRP activity could be a common response to increased formation of H₂O₂ and O₂⁻ (Pantarulo, 2005). Iron is imported into cells by transferrin and lactoferrin receptors. Transferrin level as a percentage of total protein in BAL fluid is very high (4-5.6%) compared with values for plasma (Mateos et al., 1998). Transferrin is produced and secreted at high levels in the lung seeming a major extracellular antioxidant in the lung. However, some of the iron carried by transferrin is not sequestered within ferritin, but rather, released into a catalytically active low molecular weight pool which allows the metal to catalyze ROS (Ghio, 2009).

Lactoferrin is structurally and functionally related to transferrin that comes mainly from the airway rather than alveolar region (Mateos et al., 1998), however its localization as sites at which an organism interacts with its environment e.g., secretory epithelium, suggests it plays a role in metal detoxification (Lyer and Lonnerdal, 1993).

Non Transferrin Bound Iron (NTBI) can be transported into cells via transferrin independent pathways and result in the activation of iron responsive
proteins including ferritin and lactoferrin. NTBI uptake is frequently accomplished using Nramp-2 (DMT-1 or DCT-1) (Vidal et al., 1995). mRNA for DMT1 increases after lung epithelial cell exposure to iron transcriptional control of IRE isoform, provides a mechanism of regulating Nramp 2 expression to diminish oxidative stress effectively (Lee et al., 1998). Nramp2 usually colocalize with transferrin seeming a candidate for both transferrin and non-transferrin-dependent uptake of iron. Ferrireductase activity is required prior to NTBI uptake
and expression of cytochrome b also appears to increase with iron exposure (Ghio, 2009). Superoxide can participate in ferrereduction in lung epithelial cells through ascorbatemediated cyt b ferrereduction (Ghio et al., 2003). Anionexchange protein is a novel system in the lung for transferring-independent iron transport, which superoxide dismutase significantly decrease iron import (Ghio et al., 2003; Turi et al., 2004). Export of intracellular metals can be mediated by either ferritin or transferrin release (Ghio, 2009). Release of ferritin from alveolar macrophages in BAL provides a mechanism to diminish iron stress (Wesselinus et al., 1994). Metal transporter protein 1 (MTP 1) or ferroportin 1 which present mainly in the apical membrane of airway epithelium, release iron to either the airway or the alveoli rather than to the blood for systemic distribution (Yang et al., 2005), however, ferrireduction is required before transport which is done mainly by O$_2^-$. Anion Exchange 2 (AE2) may also play a part in this release of metal (Yang et al., 2002).

Epithelial lining fluid contain several enzymatic and non-enzymatic antioxdiant systems such as extracellular forms of superoxide dismutase (Su et al., 1997), glutathione peroxidase (Aissar et al., 1996), catalase (Cantin et al., 1999) as well as several metal-binding proteins (transferrin, ceruloplasmin and lactoferrin) that minimize involvement of transition metal ions in oxidant reaction (Cantin et al., 1999). Gland cell take up plasma and interstitial uric acid and secret it along with lactoferrin into the ELF (Pedan et al., 1993) where uric acid scavenges inhaled oxidants, reacts with singlet oxygen and also prevents oxidation of GSH and ascorbic acid by chelating transition metal ion (Davies et al., 1986).

In pathological condition, all these defenses overwhelmed and in presence of high oxygen concentration, iron result in production of powerful free radicals especially hydroxyl radical which can damage major macromolecules (lipid, DNA, protein) and lead to cell death.

Some studies demonstrate role of iron in lung oxidative injury and hyperoxia. Yang et al. (1999) proved that there was no increase in the levels of intracellular antioxidants, inflammatory cytokines and hemeoxygenase-1 in the hypotransferrinemic mouse lung exposed to hyperoxia (95% O$_2$) compared with those in wild-type mice, however there were elevated expression of ferritin and lactoferrin in the lung of hypotransferrinemic mice, especially in the alveolar macrophages. The degree of iron sequestration in transferrin was greatly increased in epithelial lining fluid (from 24 to 80%) but not in serum (remained 24%) of animals with respiratory failure, suggesting that the iron originated in the lung compartment (Hallman et al., 1994). Instillation of iron containing particles into airways resulted in an increased production of ferritin and lactoferrin and declined transferrin concentrations (Ghio et al., 1998). Hemeoxygenase is responsible for the metabolism of heme imported from the extracellular space; thereby liberate carbon monoxide, bilirubin and ferrous iron. Bilirubin which has been shown to be a potent antioxidant, with albumin-bilirubin complexes being very efficient scavengers of free radicals (Voget et al., 1995). Intracellular free iron is sequestered by ferritin and the induction of ferritin by oxidants appear to be coupled to induction of HO-1, there are two isozymes of HO; HO-1 is the inducible enzyme that is induced by oxidants, whereas HO-2 is considered constitutive (Maines, 1988), recently a third isoenzymes, HO-3 which is similar to HO-2 has been described (McCoubrey et al., 1997). HO-1 expression in the rat lungs was shown to be increased following 24 to 72 h of a hyperoxic insult (Fogg et al., 1999).

Dennery and coworkers in a study exposed HO-2 null mutant mice to >95% O$_2$ and compared with wild type controls. Similar basal levels were observed, except that the knockout had a twofold increase in total glutathione content and also were sensitized to hyperoxia-induced oxidative injury and mortality (Dennery et al., 1998). Wesselinus et al. (1996) showed that there was dose dependent accumulation of iron and ferritin synthesis in alveolar macrophages exposed to iron-supplemented media. Exposure to hyperoxia (60 and 95% O$_2$) also decreased iron uptake and to a great extent ferritin synthesis by AM in iron-supplemented media. These data suggest that iron uptake promote hyperoxic injury to AM and the hyperoxia impairs the capacity of AM to sequester iron in ferritin. Therefore iron was increased in lung where it catalyzes oxidative stress contributing to lung injury. Thus lung must have a delicate method for detoxifying iron to prevent its deleterious effects.

**Role of iron chelator:** Iron chelation has been recently used for conditions without iron overload such as neurodegenerative, infectious, reperfusion injury, cardioprotection and others suggesting the role of iron as an oxidative-induced injury (Hershko, 1994; Kontogioghes et al., 2010). Desferrioxamine (DFO) has a very high affinity for Fe$^2+$ and is very efficient in preventing its reduction to Fe$^{3+}$ and the participation of iron in the Haber-Weiss reaction. DFO is a Hexideinate chelator. The maximal coordination of iron is six, so DFO binds to all sites and completely deactivate free iron (Hershko, 1992). DFO has been used in some diseases for prevention or reduction of oxidative stress induced injury (Deboer and Clark, 1992; Drossos et al., 1995; Menasche et al., 1987; Omar et al., 1989;
Paraskevaidis et al., 2005; Prass et al., 2002), but few of these studies related to lung injury. For example, combination of N-acetylcysteine plus DFO decreased bronchoalveolar lavage (BAL) fluid protein such as carbonyl protein, inflammatory cells, oxidative damage variables and proinflammatory cytokines in rat after induction of acute lung injury by instillation of lipopolysaccharide. Ritter and coworkers concluded that this combination significantly attenuated lung oxidative damage, mitochondrial superoxide production and histopathological alterations in lung (Ritter et al., 2006). In another study, 42 male Wistar rats exposed to coal dust by intratracheal instillation N-acetylcysteine (20 mg/kg/day) alone or in combination with DFO (20 mg/kg/day) could decrease the inflammatory response and the oxidative stress parameters in these rats (Pintoa et al., 2005). Aerosolized DFO could prevent severe pulmonary failure in sheep exposed to burning cotton towling (Lalonde et al., 1994). DFO due to very poor oral bioavailability and a short half-life must be administered by subcutaneous or intravenous infusion. New long acting oral agent such as deferiprox is a tridentate molecule containing 3 active binding sites for iron and has a binding ratio with 2:1 Fe<sup>2+</sup> (Stumpf, 2007). This drug has better side effect profile in comparison with defereroxamine because of its small size and lipophilic structure that could chelate intracellular iron better than defereroxamine. So, it could be a promising agent for chelation of iron in situation other than thalassaeemia (Vanorden and Hagemann, 2006). Currently authors of this paper have a clinical trial ongoing about usefulness of DFO in clinic that its primary results have been promising and is thought to be completed by end of 2010.

CONCLUSION

Oxygen therapy is one of the necessary parts of management of critically ill patients, especially with respiratory failure, but oxygen act as two edge sword in these situations and through oxidative stress process damage to major macromolecules that lead to cell death. Different pathways and molecules that involved in this process are the target of different drugs for prevention or treatment of harmful effect of oxygen. Despite favorable effects of these drugs, they are not completely successful in this condition. Regarding adequate evidence about role of iron in mediating of oxidative stress in hyperoxic conditions, protective effects of iron chelators should be considered reasonable. There are some evidences about positive effects of desferrioxamine alone or in combination when tested in animal models of lung injury or in human but they are not convincing. Further studies are necessary to clarify the importance of intervention with deferrioxamine or new long acting oral agent deferasirox and their risk/benefit in hyperoxia-induced lung injury.

REFERENCES


