Commentary

Herbert P. Wiedemann, MD, Department of Pulmonary Disease, The Cleveland Clinic Foundation, comments: Pulmonary damage is the most important adverse effect of bleomycin, an antineoplastic agent introduced in 1975 following demonstration of its efficacy against squamous cell carcinomas, lymphomas, and testicular cancers.[1] In many animal species, bleomycin induces a dose-dependent and often highly predictable interstitial pneumonitis and pulmonary fibrosis.[2] Bleomycin-induced lung injury has become widely used in animal models to study pulmonary fibrosis.

Patients receiving bleomycin are most likely to experience pulmonary damage at a cumulative total dose above 450 to 500 units. However, lung damage may occur at lower doses, especially when bleomycin is used in conjunction with other cytotoxic drugs or radiation therapy, administered either concurrently or previously (the "recall phenomenon").[2] Oxygen therapy is also widely believed to produce synergistic toxicity with bleomycin.

In this issue, Sogal and colleagues report a strong dose-dependent interaction of hyperoxia (inspired oxygen concentrations of 30%, 40%, and 50%) with bleomycin (at two different doses) in mice. Toxicity was assessed through analysis of histopathologic changes in lung sections, hydroxyproline content of lung tissue (an index of collagen deposition and fibrosis), and overall mortality. This carefully designed and executed investigation confirms and advances the findings of other groups using similar animal experiments.[2]

Oxygen alone in high concentration is independently toxic to the lung.[3,4] Molecular oxygen, although not a very reactive molecule, does produce small quantities of superoxide anion and, subsequently, the other reactive free radical intermediates, hydrogen peroxide and hydroxyl radical. These substances are highly destructive of living cells. Of note, when bleomycin is incubated in vitro with iron in the presence of oxygen, superoxide anion is generated.[5] Such an interaction provides a plausible explanation for the observed synergy between bleomycin and oxygen. In fact, one study demonstrated that *hypoxia* provided relative protection against bleomycin toxicity in rats.[6]

It is difficult to provide precise guidelines for the clinician regarding safe levels or duration of supplemental oxygen therapy in patients who have received bleomycin. However, it is prudent to limit the use of oxygen to the lowest concentration that provides an acceptable degree of oxygenation of arterial blood. This approach is supported by continued evidence of the adverse effects in normal lungs of even relatively brief periods of hyperoxia. Normal volunteers who breathe 95% oxygen for 16 hours have a significant, although reversible, alveolar-capillary leak and an enhanced release of fibrogenic factors from alveolar macrophages.[7] Patients who are ventilated with 50% oxygen for 16 to 24 hours following aortocoronary bypass surgery experience a greater degree of venous admixture, reflecting pulmonary gas exchange dysfunction, than similar patients ventilated with less than 30% oxygen.[8]

Clinicians are advised to heed the concern expressed by Joseph Priestley, one of the codiscoverers of oxygen 200 years ago, that oxygen "might burn the candle of life too quickly, and too soon exhaust the animal powers within."[4,9]

References

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