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Hyperbaric Contraindicated Chemotherapeutic Agents

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Introduction

Oxygen at high doses or under pressure should be viewed as a drug with its own set of toxicities as well as drug interactions. Hyperbaric oxygen therapy is oxygen administered at both elevated doses and elevated pressures. Hyperbaric oxygen therapy is 100% oxygen administered at one and a half to three times the atmospheric pressure at sea level. It is used to treat a variety of different conditions including but not limited to carbon monoxide poisoning, decompression sickness, arterial gas embolism, radiation-induced tissue injury, necrotizing fasciitis, osteomyelitis, problem wounds, thermal burns, etc.

Untreated pneumothorax remains the only absolute contraindication to hyperbaric oxygen treatment. However, there are many drugs with a side effect profile that could be exacerbated by hyperbaric oxygen, and the relative contraindications of chemotherapeutic drugs with hyperbaric oxygen therapy will be the focus of this article. Hyperbaric oxygen therapy is frequently used in the treatment of post-radiation injuries, and many of these patients have also undergone chemotherapy as a part of their treatment regimen, raising the concern for potential side effects with hyperbaric oxygen. A careful review of current and past medications is important when deciding to treat with hyperbaric oxygen—three drugs to evaluate include bleomycin sulfate, doxorubicin, and cis-platinum (cisplatin).

Issues of Concern

Bleomycin sulfate is a chemotherapeutic agent used to treat various tumors such as squamous cell carcinomas, lymphomas, testicular carcinomas. It is also used for pleurodesis to treat malignant pleural effusions and prevent recurrence of pleural effusions. It is a cytotoxic drug that exerts its effects via DNA scission by utilizing ferrous irons and oxygen free radicals, causing ultimate disruption during the G2 phase of the cell cycle. In addition to serious hypersensitivity or anaphylactic reactions, bleomycin-induced pulmonary toxicity is a dramatic adverse effect of this drug.[1]

Bleomycin is inactivated within cells by the enzyme aminohydrolase. This enzyme has extensive distribution throughout the body; however, it is only present in low concentrations within the skin and the lungs, which explains the predominant toxicities of bleomycin at those sites. Drug-induced pulmonary diseases cover the spectrum of different pathophysiologic conditions of the respiratory tract. Bleomycin is the best-studied cytotoxic pulmonary toxin.

Pulmonary toxicity is the dose-limiting toxicity of bleomycin therapy with a reported incidence of approximately 4%, and a mortality rate as high as 20 to 25%. Risk factors for this complication include the cumulative dose of medication, patient age, bleomycin use in multi-drug regimens, particularly with cyclophosphamide, concurrent use of radiation therapy, and supplemental oxygen therapy.[2] Experimental studies with rats produced data that showed synergism in pulmonary toxicity when rats had exposure to 100% oxygen and bleomycin compared to control or bleomycin alone.[3][4]

However, despite this theoretical risk, there have been no documented cases of pulmonary bleomycin toxicity from hyperbaric oxygen therapy. Alternatively, many patients who have had previous treatment with bleomycin have successfully received treatment with hyperbaric oxygen without sequelae. There is no firmly established timeline for when oxygen therapy appears to be safe after bleomycin administration, but, there is a consensus that as long as the patient has no signs of pulmonary compromise from fibrosis and that is has been at least three to four months since treatment with bleomycin, exposure to hyperbaric oxygen should not be considered a contraindication.

Doxorubicin is a cytotoxic anthracycline antibiotic that intercalates between base pairs of the DNA/RNA strand, inhibiting DNA and RNA synthesis, thereby preventing replication of rapidly growing cells. Doxorubicin is used in the treatment regimens for various cancers, some of which include: lymphomas, breast cancer, and sarcomas. Cardiomyopathy is the most crucial long-term toxicity, and it may manifest with acute or chronic effects. Acutely it may cause EKG changes with ST and T wave abnormalities and arrhythmias. Chronically it may progress to congestive heart failure, with this being cumulative dose-related toxicity. Doxorubicin is a contraindication with hyperbaric oxygen due to enhanced drug toxicity. An experimental study with rats produced data showing there was an 87% mortality rate in rats that were exposed to hyperbaric oxygen while concomitantly receiving doxorubicin, and it was postulated to be due to cardiac toxicity.[5]

However, there are additional experimental animal studies that did not find any increased rate of mortality but instead produced data showing increased wound healing and less cardiac cellular damage in rats that received IM injections of doxorubicin with subsequent hyperbaric oxygen therapy than with doxorubicin alone.[6]

There is an additional study, a long-term follow-up study, looking at patients with locally advanced breast cancer undergoing hyperbaric oxygen therapy before neoadjuvant chemotherapy. Clinical and pathological responses were the same in both groups (hyperbaric oxygen plus doxorubicin versus doxorubicin alone). The 5-year survival was 73%, and the mortality rate was cancer-related, with no difference between the groups.[7] Due to the potential harm and overall lack of strong evidence, clinicians should avoid using hyperbaric oxygen therapy and doxorubicin in combination. Doxorubicin has a half-life of 20 to 48 hours. Given this relatively short terminal half-life, current recommendations suggest a minimum of three days after the administration of doxorubicin before starting hyperbaric oxygen treatment.

Cis-Platinum (cisplatin) is a chemotherapeutic agent used together with other medications to treat many different cancers, some of which include: bladder, testicular, and ovarian cancer. It is an alkylating agent that becomes activated once it enters the cell. It forms interstrand and intrastrand crosslinks, interfering with normal mechanisms of replication, causing DNA damage, and ultimately resulting in apoptosis. Due to its mechanism of action, it also affects fibroblast production and collagen synthesis, which are necessary for wound healing.[8]

There have been animal experimental trials that produced data showing that mice who had exposure to cisplatin, wound breaking strength was adversely affected by the hyperbaric oxygen therapy when compared to controls. Other animal studies show hyperbaric oxygen therapy has variable effects on improving the nephrotoxic and ototoxic effects of cisplatin.[9][10][11]

Poor wound healing is one of the most common indications for hyperbaric oxygen therapy. Therefore, patients with poor wound healing should not be treated with hyperbaric oxygen and cis-platinum simultaneously. However, when wound healing is not a goal of treatment and time to treatment is crucial, such as in carbon monoxide poisoning, arterial gas embolism, central retinal artery occlusion, and others. Hyperbaric oxygen is indicated in these emergencies.

Clinical Significance

There are many drugs with a side effect profile that could be exacerbated by hyperbaric oxygen. Hyperbaric oxygen therapy is frequently used in the treatment of post-radiation injuries, and many of these patients have also undergone

chemotherapy as a part of their treatment regimen, raising the concern for potential side effects with hyperbaric oxygen. Three important drugs to evaluate:

- **Bleomycin**: Pulmonary toxicity is the reason concurrent use of bleomycin and hyperbaric oxygen therapy is contraindicated. It is considered safe to proceed with hyperbaric oxygen treatment if it has been at least three to four months post bleomycin administration.
- **Doxorubicin**: Cardiac toxicity is the reason concurrent use of doxorubicin and hyperbaric oxygen therapy is contraindicated. It is considered safe to proceed with hyperbaric oxygen treatment if it has been at least three days post doxorubicin administration.
- **Cisplatin**: Impaired wound healing is the reason concurrent use of bleomycin and hyperbaric oxygen therapy is contraindicated. Proceed with treatment in emergent situations and when it has been an extended period from cisplatin administration.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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