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CASE REPORT

Bleomycin and scuba diving: to dive or not to dive?

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ABSTRACT

Bleomycin is to treat patients with testicular cancer and lymphoma. Bleomycin can bind to DNA and chelate iron. The resulting complex can form an intermediate capable of interacting with oxygen to produce reactive oxygen species, particularly superoxide. Administrating high-inspired oxygen concentrations (e.g. during anaesthesia or acute illness) has been reported to exacerbate pulmonary injury. The duration of risk after bleomycin chemotherapy is unknown. Here we discuss our advice to a young male patient, who was successfully treated with bleomycin for testicular cancer, concerning the safety to return to scuba diving. Since scuba divers are exposed to high partial oxygen pressures (depending on the depth of the dive) we discouraged this patient from resuming scuba diving.

INTRODUCTION

Bleomycin is given in the standard regimen for treating testicular cancer. The incidence of fatal pulmonary toxicity in this low-risk population of young male patients is approximately 2 to 3%. Patients treated with bleomycin are sensitive to oxygen-mediated lung injury. Here we discuss a question patients frequently ask concerning the safety of returning to scuba diving following bleomycin therapy.

CASE REPORT

A 35-year-old man was admitted to our hospital because of a painless enlargement of the left testis, without further symptoms. Ultrasonography demonstrated a solid mass in the left testis. Laboratory examination showed an elevated serum chorionic gonadotropin (β-hCG) of 1100 IU/l (normal: <2) and a serum lactate dehydrogenase of 520 IU/l (normal: 160-320); serum alfa-foetoproteine was normal. Chest X-ray was normal. CT scan of the abdomen showed retroperitoneal lymphadenopathy (maximal diameter 6 cm). The patient proceeded to inguinal orchidectomy with removal of the affected testis. Histopathologically the removed testis consisted of choriocarcinoma. Since this patient had a stage IIC carcinoma with a good prognosis, he was treated with three courses of BEP (bleomycin, etoposide and cisplatin). No pulmonary toxicity was observed. Subsequent radiographic evaluation showed no residual disease and tumour markers normalised. At this time our patient, who used to be an active scuba diver, asked whether it was safe to return to scuba diving after having undergone chemotherapy containing bleomycin. We will discuss our considerations based on a literature search.

BLEOMYCIN

The bleomycins are a family of cytotoxic glypeptide antibiotics isolated from *Streptomyces verticullis*, with a molecular weight of approximately 1500 D. All contain a unique structural component, bleomycinic acid, and differ only in their terminal alkylamine group. Bleomycin A2, the predominant peptide, and a series of analogues are prepared by total chemical synthesis.[1] The primary biochemical action of the A2 peptide is to produce single- and double-strand breaks in DNA. This breakage is reflected in the chromo-

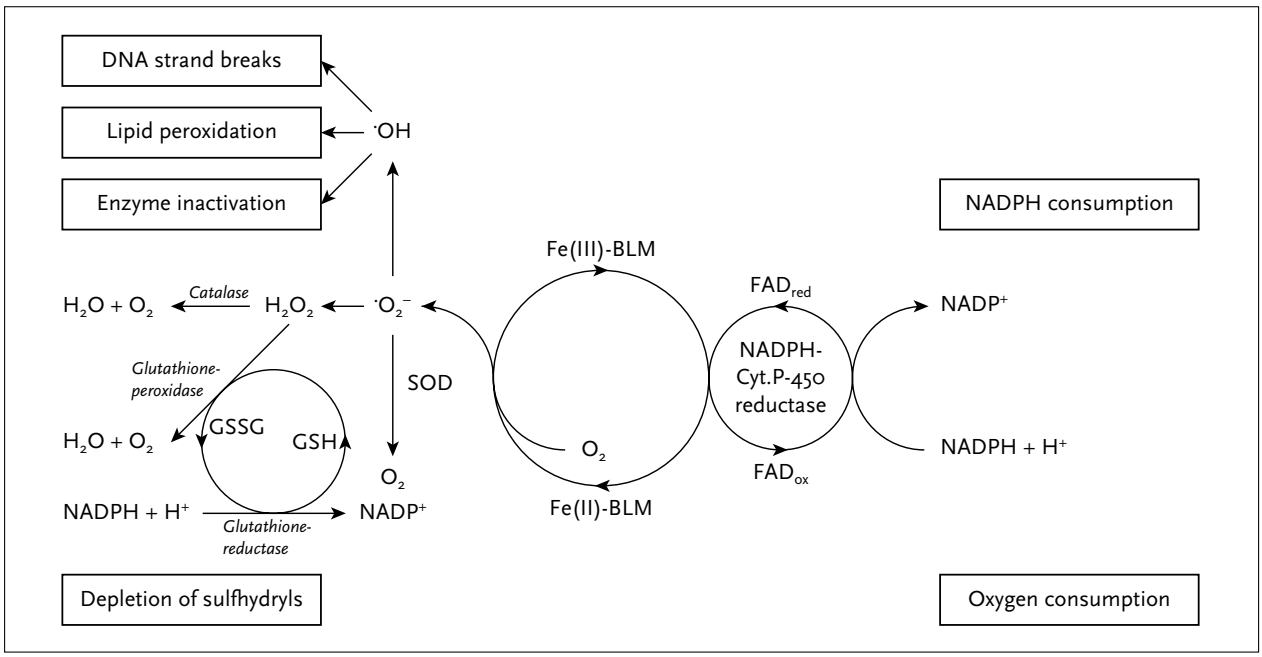

Figure 1

Redox cycling of the iron bleomycin complex with subsequent 'oxidative stress' caused by the formation of reactive oxygen species (superoxide radical $\cdot O_2$-, hydroxyl radical $\cdot OH$, hydrogen peroxide H_2O_2), potentially toxic reactions and enzymatic detoxification mechanisms

SOD = superoxide dismutase, GSSG = oxidised glutathione, GSH = glutathione, NADPH = nicotinamide adenine dinucleotide phosphate (reduced form), NADP+ = nicotinamide adenine dinucleotide phosphate (oxidised form), FADred = flavin adenine dinucleotide (reduced form), FADox = flavin adenine dinucleotide (oxidised form), BLM = bleomycin.

somal gaps, deletions and fragments seen in cytogenetic studies of whole cells. The mechanism of DNA breakage has been clarified by investigation of the action of bleomycin on both viral and mammalian DNA and results from the production of free radicals by an Fe(II)-bleomycin complex intercalated between opposing strands of DNA (see *figure 1*). The initial step in this reaction sequence seems to be the production of an activated bleomycin-Fe(II)-O_2 complex. The activated complex then binds to DNA. At saturating concentrations of bleomycin, one molecule of drug is bound per four to five base pairs of DNA.[2] The second step in the action of bleomycin is the induction of DNA breaks, mediated by free radicals produced by the activated bleomycin-Fe(II) complex. The importance of Fe(II) is indicated by the observation that iron-chelating agents inhibit the DNA scission reaction.[3] The enzyme-like bleomycin-Fe(II) complex induces the reduction of molecular oxygen to superoxide and hydroxyl radicals.[4] In this process, Fe(II) undergoes oxidation to Fe(III). The hypothesis that oxygen radicals participate in the DNA cleavage mediated by bleomycin is based on several observations. First, strand breakage requires the presence of O_2 and ceases in an anaerobic environment.[5,6] Second, the oxidation of bleomycin-Fe(II) requires oxygen consumption.[3] Finally free-radical scavengers and superoxide dismutase (which inactivate O_2 radicals) inhibit DNA strand breakage in *vitro*[7] and pulmonary toxicity *in vivo*.[8]

BLEOMYCIN AND PULMONARY TOXICITY

Intracellular bleomycin is inactivated by an aminohydrolase that is found in both normal and malignant cells.[9] The enzyme cleaves the carboxamide amine from the β-aminoalaninamide, yielding a weakly cytotoxic deamido-bleomycin. Interestingly, this enzyme is present in relatively low concentrations in lung and skin, the two normal tissues most susceptible to bleomycin damage.[10] Several distinct pulmonary syndromes have been associated with the use of bleomycin, such as bronchiolitis obliterans with organising pneumonia (BOOP), eosinophilic hypersensitivity and, most commonly, interstitial pneumonitis.[11] In its later stages interstitial pneumonitis can be complicated by progressive interstitial fibrosis, hypoxia and death. Pulmonary toxicity, usually manifesting with cough, dyspnoea and bibasilar pulmonary infiltrates on chest X-ray film, occurs in 3 to

5% of patients receiving a total dose of less than 450 units of bleomycin, increasing significantly to a 10% incidence in those treated with greater cumulative doses.[12] Although the risk of lung toxicity increases with cumulative doses greater than 450 units, severe pulmonary sequelae have been observed at total doses below 100 units. In the standard regimen for treating testicular cancer, bleomycin is given in doses of 30 units weekly for 9 to 12 doses, and the incidence of fatal pulmonary toxicity in this low-risk population of young male patients is about 2 to 3%.[13,14] Pulmonary function tests, particularly the carbon monoxide diffusing capacity, are of possible value in predicting a high risk of pulmonary toxicity. However, most patients treated with bleomycin show a progressive (10 to 15%) deterioration in diffusion capacity with increasing total dose and a more marked increase in changes above 240 units total dose. It is not clear whether the diffusion capacity test can be used to predict which patients will subsequently develop clinically significant pulmonary toxicity.[15] In advanced stages in the evolution of bleomycin pulmonary toxicity, the diffusion capacity as well as arterial O_2 saturation and total lung capacity become markedly abnormal. Besides the total dose of bleomycin given, various other factors have shown to increase the pulmonary toxicity of bleomycin: prior radiation of the lung parenchyma,[16,17] administration of high fractional-inspired oxygen concentration,[18-22] the age of the patient[23] and renal insufficiency (bleomycin is cleared by the kidneys).[24] The sensitivity of bleomycin-treated patients to high concentrations of inspired O_2 is intriguing in view of the molecular action of bleomycin, which is dependent on, and mediated by, the formation of oxygen-derived free radicals. Goldliner *et al.* observed five testicular tumour patients treated with 135 to 595 units of bleomycin 7 to 12 months earlier who underwent retroperitoneal lymph node dissection or resection of pulmonary metastases while receiving an intraoperative fractional concentration of inspired oxygen (FIO_2) ranging from 0.35 to 0.42.[18] All five developed respiratory failure postoperatively and died.[18] A reduction in inspired O_2 to an FIO_2 between 0.22 and 0.25, and a decrease in fluids administered during surgery, prevented mortality in subsequent patients.[18] It has been shown that a greater degree of experimental lung injury with oxygen was found at 8 versus 21 days following intratracheal bleomycin.[25] Nevertheless, in the above-mentioned report by Goldiner *et al.* the mean time between bleomycin administration and surgery was 9.6 months.[18] Thus, the period of time when oxygen administration appears to be safe following bleomycin has not been established. Therefore, current safeguards for anaesthesia of bleomycin-treated patients (both with a history of bleomycin toxicity and even those with previous drug exposure without clinical toxicity) include the use of the minimal tolerated concentration of inspired oxygen and modest fluid replacement to prevent pulmonary oedema.[26]

SCUBA DIVING

Very few scuba divers, and even fewer sport scuba divers, use oxygen in their tanks. The vast majority of sport divers use compressed air (21% oxygen). The partial inspiratory oxygen pressure (PIO_2) is a function of the fractional concentration of inspired oxygen (FIO_2), the barometric pressure (PB), and the partial pressure of water vapour (PH_2O) in humidified gas; that is $PIO_2 = FIO_2 (PB - PH_2O)$.[27] So the partial pressure of oxygen in the inspired (compressed) air is a direct function of the depth of the dive. For every 9.9 m depth of a seawater dive, the ambient barometric pressure to which the diver is exposed increases by 1 atm. At a dive depth of 19.8 m of seawater (3 atm total pressure), the partial pressure of inspired oxygen in a scuba diver breathing compressed air is 0.63 atm, equivalent to breathing 63% oxygen on the surface. At a dive depth of 29.7 m of seawater, not an unusual depth for many sport divers, the partial pressure of oxygen is 0.84 atm, equivalent to breathing 84% oxygen on the surface.

ADVICE REGARDING PREVIOUS TREATMENT WITH BLEOMYCIN AND SCUBA DIVING

Several clinical and animal studies strongly support the relationship between bleomycin toxicity and oxygen therapy. However, there are no data on what time interval is safe between the last dose of bleomycin and oxygen therapy. Bleomycin is especially successful in the BEP (bleomycin, etoposide, cisplatin) regimen against testicular cancer. These young men frequently ask whether it is safe to resume scuba diving. However, the partial pressure of inspired air is dependent on the barometric pressure, which is a direct function of the depth of the dive. Therefore, these patients should be advised that theoretically there is a risk of developing pulmonary damage due to exposure to a higher partial pressure of inspired oxygen while scuba diving. However, published data regarding the safety of exposure to high concentration oxygen during recreational activities such as scuba diving are limited and patients should be counselled that safety cannot be assured during these activities.[28] Since the period of time when oxygen administration appears to be safe following bleomycin has not been established (see above) we think scuba diving should be discouraged, even several years after bleomycin treatment.

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