Safe administration of hyperbaric oxygen after bleomycin
A case series of 15 patients

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ABSTRACT

Introduction: Supplemental oxygen has been reported to cause pulmonary complications after bleomycin. We describe the safe administration of hyperbaric oxygen (HBO_2) after bleomycin in 15 patients.

Methods: Paper and electronic records were reviewed for bleomycin-exposed patients at the Duke Center for Hyperbaric Medicine and Environmental Physiology from 1979 to 2010.

Results: Fourteen bleomycin-exposed patients received HBO_2 at Duke under a special-precautions protocol. One was treated for DCS elsewhere. The protocol included: pretreatment evaluation; chest radiograph; spirometry; blood gases; a single, 2-atmospheres absolute (atm abs), 120-minute HBO_2 treatment; and a gradual acceleration over one week to a twice-daily schedule contingent on clinical and laboratory findings. Bleomycin indications were: head-and-neck squamous cell carcinomas (11), Hodgkin's lymphoma (2), other carcinomas (2). HBO_2 indications were: osteoradionecrosis (10), soft-tissue radionecrosis (3), DCS (1) and a provocative oxygen toxicity test for a military aviator (1). Total bleomycin doses ranged from 40 to 225u/m^2 (mean ± SD, 105 ± 57) given in conjunction with other chemotherapies and/or radiation. Radiation was 63.3 ± 31.72 Gy (mean ± SD), none to the chest with the exception of one patient treated for DCS elsewhere. Other chemotherapies included: vinblastine (11), methotrexate (11), CCNU (6) cisplatinum (7), dacarbazin (2), Adriamycin (1), and vincristine (1). Median age at time of HBO_2 was 52 years (range 22-77). Median bleomycin-to-HBO_2 latency was 34 months (range 1-279). Three patients received HBO_2 within six months, and seven patients received HBO_2 within two years of their last bleomycin exposure. There were no adverse pre-to-post HBO_2 changes in: arterial blood gases, spirometry, chest radiograph findings or clinical reports. There were no persistent post-HBO_2 pulmonary complications on follow-up. Post-HBO_2 data were available for 40%, 53%, 87% and 100% of these parameters respectively.

Discussion: Bleomycin and oxygen can individually cause acute pulmonary toxicity. However, evidence for increased long-term susceptibility based on their synergy may be overstated.

INTRODUCTION

Controversy has surrounded the practice of supplemental oxygen administration to perioperative patients who have received bleomycin chemotherapy since the publication of a five-patient case series by Goldiner in 1978 [1] that suggested an oxygen-related risk of severe pulmonary complications. Although a PubMed search revealed no articles specifically stating that hyperbaric oxygen therapy (HBO_2) should be prohibited after bleomycin, diving-related hyperbaric oxygen exposure was unambiguously advised against by several prominent pulmonary and diving experts in a series of articles and letters in the literature of the late 1980s [2-4]. Although more recent articles have argued that perioperative oxygen restriction is not necessary [5-7], controversy has persisted [8-10], and as late as 2008, prior bleomycin remained an absolute contraindication to HBO_2 therapy in a highly influential hyperbaric medicine textbook [11]

no matter how long the interval between bleomycin and HBO_2. Therefore, in an effort to provide additional data on this issue we report a case series of 15 post-bleomycin patients who safely received HBO_2 from 1979 to 2010 at the Duke Center for Hyperbaric Medicine and Environmental Physiology under a special-precautions protocol.

METHODS

After IRB approval, Duke Hospital and Duke Hyperbaric Center electronic records were searched from 1970 to 2010 for patients with a history of bleomycin administration who had presented for HBO_2 therapy. Both the electronic and paper records of these patients were examined for initial bleomycin and HBO_2 indications, bleomycin dose, therapeutic radiation to the thorax (yes or no), time elapsed between bleomycin therapy and the first HBO_2 treatment (bleomycin-to-HBO_2 latency in months), the number of HBO_2 sessions, concurrent (with HBO_2) chemotherapy, age, gender and smoking history.

The electronic and paper records were then searched for imaging and laboratory tests (arterial blood gas values, spirometry, chest radiograph reports) and progress notes that addressed post-HBO_2 respiratory status. Post-HBO_2 pulmonary complications were defined as any adverse change from pre-HBO_2 treatment condition in pulmonary imaging, laboratory values or progress note entry not attributable to the underlying disease. The elapsed time between the date of the last bleomycin treatment and the first HBO_2 treatment was calculated and designated as the bleomycin-to-HBO_2 latency time. The elapsed time between the date of the first HBO_2 treatment and the latest chart entry with pulmonary-related data was calculated and designated as the total follow-up time.

RESULTS

Fifteen records from bleomycin-exposed patients who had received HBO_2 were located. Fourteen records corresponded to bleomycin-exposed patients who had received HBO_2 at Duke under the protocol. The protocol included: pre-treatment evaluation; chest radiograph; spirometry; arterial blood gases; a single 2-atm abs, 120-minute HBO_2 treatment; and a gradual acceleration over a one-week period to a twice-daily schedule contingent on clinical and laboratory findings. The records of one additional bleomycin-exposed patient who was treated with HBO_2 for decompression sickness at another institution and later evaluated at Duke for fitness to dive was also reviewed. Initial bleomycin indications were: head-and-neck squamous cell carcinomas (11), Hodgkin's lymphoma (2) and other carcinomas (2). Indications for HBO_2 after bleomycin were: osteoradionecrosis (10), soft-tissue radionecrosis (3), DCS (1) and a provocative oxygen toxicity test for a military aviator (1). Total bleomycin doses ranged from 40 to 225u/m^2 (mean ± SD, 105 ± 57) given in conjunction with other chemotherapies and/or radiation. Radiation was 63.3 ± 31.72 Gy (mean ± SD), none to the chest except in the one patient who was treated for DCS elsewhere.

Other chemotherapies included: vinblastine (11), methotrexate (11), CCNU (6) cisplatinum (7), dacarbazin (2), adriamycin (1) and vincristine (1). Median age at time of HBO_2 was 52 years (range 22-77 years). Median bleomycin-to-HBO_2 latency was 34 months (range 1-279). Forty-seven percent of the sample received HBO_2 within two years of bleomycin chemotherapy without adverse effects *(Table 1, facing page)*.

There were no persistent post-HBO_2 pulmonary complications *(Table 2, facing page)*. One patient reported chest wall pain following one hour of HBO_2 that resolved after a 15-minute air break. This patient remained well and went on to receive a total of 38 treatments. A second patient experienced a transient episode of reduced PO_2 and chest pain that was not considered clinically significant and resolved within six hours of that day's HBO_2 treatment. This patient went on to receive a total of 40 treatments and remains well 21 years later. There were no adverse pre-to-post-HBO_2 changes in: arterial blood gases, spirometry, chest X-ray findings or clinical reports. Post-HBO_2 data were available for 40%, 53%, 87% and 100% of these parameters respectively. There were no persistent post-HBO_2 pulmonary complications on follow-up.

DISCUSSION

The antineoplastic agent bleomycin is an antibiotic mixture of low-molecular weight glycopeptides, first isolated from *Streptomyces verticillus* in 1966 by Hamao Umezawa [12]. Bleomycin's antineoplastic activity results from DNA strand scission from reactive oxygen species generated by iron binding and oxidation-reduction cycling [13,14]. Bleomycin's minimal myelosuppressive action [15-17] makes it particularly well suited as a component of a multiagent chemotherapy drug regimen; it is used for testicular cancer, lymphomas, sarcomas, melanomas, squamous cell carcinomas and as a sclerosing agent for malignant pleural effusions.

TABLE 1 – *Demographics, bleomycin indications, adjuvant chemotherapy and ordered by bleomycin-to-HBO_2 latency*

Patient number	Age at HBO_2	Gender	Bleomycin Indication	Bleomycin dose	Other chemotherapy received	Beomycin-to-HBO_2 latency (months)
1	77	m	nasal scca	40	vinblastin, methotrexate, CCNU	169.3
2	38	m	other	unknown	vincristine	279.5
3	29	f	other	120	methotrexate, cisplatinum, oncovin, dexamethasone	100.1
4	57	f	nasal scca	unknown	unknown	216.7
5	24	m	Hodgkin's	40	adriamycin, vinblastin, dacarbazine	18.4
6	60	f	oral scca	90	vinblastin, methotrexate, CCNU	17
7	61	f	oral scca	120	vinblastin, methotrexate, CCNU	39.1
8	52	m	oral scca	120	vinblastin, methotrexate, cisplatinum, CCNU	23.8
9	74	f	oral scca	80	vinblastin, methotrexate, cisplatinum	5
10	54	f	nasal scca	225	vinblastin, methotrexate, CCNU	34.2
11	61	m	oral scca	120	vinblastin, methotrexate, cisplatinum	6.2
12	26	m	Hodgkin's	210	vinblastin, doxorubicin, dacarbazine	9.5
13	41	m	oral scca	60	vinblastin, methotrexate, CCNU	1.1
14	20	f	nasal scca	80	cisplatinum, methotrexate, hydroxyurea	57.6
15	43	f	oral scca	60	vinblastin, methotrexate, cisplatinum	59.2

scca = squamous cell carcinoma

TABLE 2 – *HBO_2 indication, symptoms post-HBO_2, imaging and laboratory studies, HBO_2 outcome and follow-up time*

Patient number	HBO_2 indication	Symptoms post-HBO_2	ABG post-HBO_2	CXR	Spirometry	HBO_2 outcome	Follow-up (months)
1	ORN, jaw	no		no change			0.9
2	ORN, jaw	no		no change	no change	no change	129.5
3	DCS	no		no change	no change		1.7
4	ORN, jaw	no	no change	no change	no change	no change	1.2
5	O2 test[1]	no		no info	no change	no change	0.3
6	ORN, jaw	no		no info			6.8
7	ORN, jaw	no		no change			135
8	ORN, jaw	no	no change	no change	no change	no change	158.8
9	STRN, oral	no	no change	no change			8.4
10	ORN, jaw	no	no change	no change	no change		32.2
11	STRN, oral	no	no change	no change			12.1
12	STRN, oral	yes[2]	no change	no change	no change	no change	48.8
13	ORN, jaw	no		no change			7.5
14	ORN, jaw	yes[3]	no change	no change	improved	worse	259.7
15	ORN, jaw	no		no change			219.6

nl = normal, ORN = osteoradionecrosis, STRN = soft tissue radionecrosis

1 Provocative test for increased susceptibility to O_2 toxicity in an aviator who had received bleomycin.

2 Chest wall pain reported after one hour of HBO_2 which resolved after a 15-minute air break. PO_2 110 and 77 mmHg on post-HBO_2 samples. This patient went on to receive a total of 38 treatments.

3 Transient episode of reduced PO_2 and chest pain which was not considered clinically significant and which resolved after treatment This patient went on to receive a total of 40 treatments.

Acute pulmonary toxicity of bleomycin

Acute pulmonary toxicity is a well-recognized side effect of bleomycin therapy. It has been reported in up to 40% of patients, with a fatality rate of 1.5% in some series [15,18]. Tissues with the lowest level of bleomycin hydrolase (lung and skin) are the most susceptible [19] and bleomycin pulmonary toxicity has been reported at doses as low as 20 to 60 (u/m^2) [20,21]. Risk increases rapidly above a cumulative dose of 450 (u/m^2) [15] and is greater with concomitant additional chemotherapy [22] or adjunctive radiotherapy to the chest [2,23,24].

Renal insufficiency [21,25] and age [9,15] may also increase risk. The injury is independent of the route of drug administration and appears to begin in the pulmonary vascular endothelium with edema and an influx of inflammatory cells plus fibroblasts which deposit collagen leading to interstitial fibrosis [26]. The acute toxicity syndrome is expressed as a hypersensitivity pneumonitis with eosinophilic infiltrates [27] or a dose-dependent interstitial pneumonitis that progresses to pulmonary fibrosis. Initial symptoms are fever, dry cough, dyspnea, tachypnea and cyanosis with fine bibasilar crepitations, rhonchi and pleural rubbing [15, 18]. Radiographic findings may occur in the absence of clinical symptoms [22] or at any time during their progression [28] and include bilateral bibasilar alveolar and interstitial infiltrates as well as lobar consolidation.

Unilateral findings and focal infiltrates have also been described [29]. Small CT scan linear and subpleural nodular lesions may appear early and before changes on chest X-ray, and pulmonary function may show a restrictive pattern and a decrease in diffusing capacity for carbon monoxide (DLCO) [7]. If pulmonary toxicity occurs, symptoms usually begin during bleomycin treatment. However, delayed presentations of up to six months have been reported. Cessation of drug administration has been reported to result in regression of symptoms in about one-third of the patients [18].

Reports of delayed bleomycin pulmonary toxicity associated with supplemental oxygen

Perioperative administration of supplemental oxygen was first suggested to contribute to delayed bleomycin pulmonary toxicity in 1978 when Goldiner published a series of five patients who suffered fatal postoperative respiratory failure after perioperative oxygen in the setting of prior bleomycin chemotherapy [1]. These patients had received moderately high doses of bleomycin (mean doses 426 ± 181 mg) administered a mean of 9.6 months earlier.

Although all afflicted patients had preoperative pulmonary disease with documented abnormal DLCO values (55-68% of predicted) prior to oxygen administration, Goldiner attributed the respiratory failure to perioperative oxygen supplementation (39% fraction of inspired oxygen/FiO_2, mean duration 5.86 ± 0.96 SD hours) [1]. Moreover, Goldiner subsequently published a second, non-controlled, prospective trial that limited perioperative oxygen to 24% FiO_2 and restricted crystalloid fluid replacement. All 12 patients survived, lending anecdotal credence to his supposition.

Goldiner's reports were followed by Nygaard's description of four respiratory deaths after esophageal resection in eight patients given radiotherapy (3000cGy) and bleomycin [24]; Douglas's report of a single respiratory death out of 14 patients with testicular carcinoma following high FiO_2 and rigid bronchoscopy; and case series by Luis, Hulbert, Ingrassia and Gibson [10,30-32] that appeared to establish a pattern to support oxygen contraindication after bleomycin administration.

A short history of the association between bleomycin, supplemental oxygen and respiratory failure

By the 1980s, the contraindication of supplemental oxygen after bleomycin was widely accepted. However, because a causal link between bleomycin, perioperative oxygen and postoperative respiratory failure was never firmly established, publications began to question the causal relationship proposed [5,6,33]. In a 1998 study Donat and Levy reported 77 patients undergoing 97 surgical procedures. In their retrospective study, 19 of 77 post-bleomycin patients developed postoperative oxygen desaturation after surgery. The patients' last bleomycin dose had been given 6.4 months (mean value) prior to surgery.

However, the case control comparison showed no association with intraoperative FiO_2. Units of blood transfused, preoperative forced vital capacity and surgical time (in descending order) were the only significant predictors of oxygen desaturation. All cases responded to conventional therapy, and Donat and Levy concluded that oxygen was not a significant risk factor for developing postoperative pulmonary complications [5]. Animal models of acute bleomycin toxicity rather than chronic risk have shown an adverse and synergistic effect of oxygen and bleomycin. Toledo found that bleomycin shortened the median survival time of mice breathing 40% oxygen [34], and Tryka [35] reported 90% mortality in hamsters who received concomitant normobaric hyperoxia and bleomycin therapy *vs.* 15% in those receiving

TABLE 3 – ***Literature summary: Bleomycin to perioperative oxygen latency***

Reference	Oxygen dose	Bleomycin dose	Bleomycin to O_2 latency	Outcome
1	.39 for 5.86 ± 0.96 hours	426 ± 181 mg	7 - 12 months	5 resp. failure fatalities; all with abnormal DLCO values preoperatively.
5	Mean values: 0.87 for 56 min followed by 0.4 for 8.1 hours	437 mg	Mean value 6.4 months	77 patients. No ARDS. No fatalities. Post-op desaturation in 19 patients, responding to therapy.
24	surgical FiO_2 not recorded	120 mg	unknown and variable	Respiratory failure and death in 4 of 8 patients after 3000-6000cGy radiotherapy, bleomycin and esophageal resection.
6	0.5 - 1 for 1 hour 35	300 mg	3 months	Only 1 case with respiratory failure out of 14 patients and 20 procedures with bronchoscopy with high FiO2. Responded well to steroids.
10	0.33 for 4 hours 0.71 for 30 min	240 mg	20 days	Case report. Respiratory failure; recovered with steroids.
22	> 0.33 0.4 – 0.5	360 mg 360 mg	1 month 3.5 months	2 cases of fatal progressive respiratory failure
30	0.5 for 1 hour 0.5 for 2 hours + 0.8-1 for 2 hours	30 mg	21 days 49 days	Case report. 1st procedure: No post-op problems. 2nd procedure: ARDS; died in ICU of MOF. Steroids no effect. DLCO 80% pre-op.
31	0.4 for 9.5 hours	360 mg	10 days	Case report of 1 fatal resp. failure
32	0.3 for 10 hours	120 mg	7 months	Case report. ARDS, responded well to steroids. History of pneumonitis after bleomycin.
33	0.41 ± 0.04 for 6.1 ± 0.7 hours	407 ± 20 mg	10 ± 0.3 months	13 patients. No resp. failure. Abnormal. PFTs in only 3 patients.
45	0.33 intra-op 0.4 for 4 days post-op	189 mg	19 days	Case report: Died 12 days post-op. Autopsy showed signs of bleomycin toxicity. DLCO pre-op 60%.

ARDS = Adult respiratory distress syndrome; MOF = Multiorgan failure; DLCO = diffusion capacity for carbon monoxide

bleomycin alone. However elevated oxygen partial pressure during, but not following, bleomycin therapy was the experimental risk factor in both studies, and Tryka did not find increased mortality or interstitial pneumonitis when normobaric hyperoxia (FiO_2 of 0.7 or 1) was administered after bleomycin.

It is also difficult to extrapolate animal data to humans because species differences in oxygen toxicity susceptibility [36]. The equivalency of experimental oxygen doses and the duration of experimental oxygen administration in most animal studies are greater than those used in routine perioperative patient care [34,36], making it difficult to isolate simple pulmonary oxygen toxicity from the combined effect of oxygen and the drug. Some have suggested that the practice of avoiding high FiO_2 after bleomycin be abandoned [26,37].

Hyperbaric oxygen and bleomycin

By extension and in conformity with prevailing beliefs, by the 1980s a history of bleomycin chemotherapy was an accepted contraindication to diving-associated HBO_2 exposure [2-4], and although not well supported by evidence, this contraindication has persisted [11].

However, HBO_2 has been used in close temporal proximity to bleomycin without adverse outcome. In 1983 Shanta reported on 28 patients with oral squamous cell carcinoma, who were treated with 14 cycles of irradiation in a hyperbaric chamber for 15 to 20 minutes, at 3 atm abs, three times a week after receiving 15 to 20 mg of bleomycin (totals of 150 to 200 mg) (38) without adverse effect. Wang reported a patient who completed 30 HBO_2 treatments (2 atm abs for 90 minutes) five months after a cumulative dose of 45 units of bleomycin.

Wang's patient died from her malignancy one month after treatment, but without report of pulmonary complications [39]. In 2007 Latson reported a case of a 36-year-old diver who was treated with a U.S. Navy Treatment Table 6 at 22 months after treatment with combined bleomycin (160 mg total) and neck radiation for Hodgkin's lymphoma. This patient showed no change in pulmonary function tests [40]. Gray reported a diver one year post-bleomycin therapy who returned to active diving without consequence [41], and other authors report similar observations [37,42,43]. Moreover, our 15-patient series found no post-HBO_2 pulmonary complications in spite of a wide variety of bleomycin indications, HBO_2 indications, doses, adjunctive radiation and HBO_2 latencies in the case sample.

CONCLUSIONS

This case series adds to the literature supporting the safe use of HBO_2 after bleomycin *(Table 3, previous page)* and suggests that the prohibition of post-bleomycin HBO_2 should be questioned. Although bleomycin and oxygen can individually cause acute pulmonary toxicity, we believe that the evidence for increased long-term susceptibility based on their synergy is overstated and because bleomycin is widely prescribed, unnecessary oxygen restriction has the potential to adversely impact future medical care (surgery, HBO_2 therapy), professional careers (flying, diving) and recreational activities of the subset of cancer survivors who have required this drug [3,37,43,44].

Although we do not routinely withhold oxygen therapy from post-bleomycin patients, our practice is to wait three to six months post-bleomycin administration before treating with HBO_2. Only two of our patients received HBO_2 sooner than six months after bleomycin; the majority were treated after two years: thus, we do not have strong evidence for the safety of HBO_2 sooner than six months following bleomycin. Therefore, in accordance with other experts [37], we individually evaluate each candidate. If there is any question of pre-existing pulmonary disease we establish a baseline for pulmonary function with spirometry, DLCO and imaging and monitor for adverse change during HBO_2 therapy. ■

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