

# Bleomycin Induced Pulmonary Toxicity: A Case Report

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## Abstract

Bleomycin is a potent antitumor agent that is particularly effective for the treatment of squamous cell and testicular tumors. However, its usefulness is limited by the potentially life-threatening pulmonary toxicity that has mortality between 2 to 10 % of affected patients.<sup>1, 2, 3</sup> We report a case of pulmonary toxicity developing in a patient who had previously received bleomycin therapy and subsequently underwent surgery under general anesthesia.

## CASE REPORT

A 47 year old man was hospitalized for wide local excision of squamous cell carcinoma of the lower lip. He was hypertensive, controlled on atenolol for the past four years. Personal history included tobacco and betel chewing for the past 30 years. He was a non-smoker and non-alcoholic. The patient had received chemotherapy comprising of two cycles of bleomycin 15mg/ day for four days (cumulative dose, CD, 120mg, last dose 4 months prior to admission), cisplatin (CD 240mg), and 5-fluorouracil (CD 5g). He remained asymptomatic during the course of chemotherapy. The patient also received external radiotherapy.

There was no history of dyspnea on exertion, cough or sputum production. His physical examination was unremarkable except for an anticipated difficult intubation. His mouth opening was restricted (interincisor gap 2cm) and thyromental distance 4.5 cm presumably due to submucosal fibrosis and radiotherapy, respectively. He weighed 65 kg and was 176cm tall. His blood pressure was 130/ 88 mm Hg with a heart rate of 72/min. Chest auscultation revealed clear lung fields. Cardiac examination was unremarkable. Blood investigations including hemogram, blood sugar, serum electrolytes, renal and liver function tests were in the normal range. Chest radiograph and ECG were normal.

Echocardiogram revealed a normal study with an ejection fraction of 57%.

The patient received diazepam 10mg orally the night before and two hours prior to surgery. The patient received the morning dose of antihypertensive medication. In the operation theatre standard monitoring was instituted. Blood pressure was 140/ 90 mmHg with a heart rate of 80/min.

Uneventful awake nasal fibreoptic intubation under local anesthesia was performed with a 7.5mm internal diameter PVC cuffed tracheal tube. After confirming correct placement of the tracheal tube, anesthesia was induced with propofol 120mg, fentanyl 100 $\mu$ g, and maintained with isoflurane in nitrous oxide and oxygen (FiO<sub>2</sub> 0.3) and incremental doses of morphine. Neuromuscular block was achieved with vecuronium and the lungs were ventilated to maintain Et CO<sub>2</sub> between 32 to 36mmHg. The intraoperative period (approximately 2.5h) was uneventful. The patient had stable blood pressure and oxygen saturation remained between 98 – 100%. During the intraoperative period 1200ml of Ringer's lactate solution was administered, and blood loss was approximately 200ml. At the completion of surgery, neuromuscular block was antagonized with neostigmine 2.5mg iv and glycopyrrolate 0.4mg iv after return of spontaneous respiratory efforts. Immediately thereafter the patient developed jerky respiration SpO<sub>2</sub> decreased to 89% with 100 % oxygen. Bilateral crepitations were heard on auscultation of chest and copious frothy serosanguinous fluid was detected in the tracheal tube. A presumptive diagnosis of pulmonary edema was made. Furosemide 40mg i.v. and morphine 3mg iv were administered, in addition to 100% oxygen. Neuromuscular block was reinitiated with vecuronium 6mg iv and mechanical ventilation started. The oxygen saturation improved to 95% and the patient was hemodynamically stable. However, after approximately 30min, the patients' condition deteriorated and there was an increase in tracheal serosanguinous secretions with a drop in oxygen saturation. Furosemide 20mg iv was repeated. The systolic blood pressure decreased to 70 mmHg and a dopamine infusion

was started. Blood pressure continued to decrease and an adrenaline infusion was commenced. Hydrocortisone 200 mg was administered. Blood pressure improved to 100/70 mmHg with a heart rate of 140/min, SpO<sub>2</sub> 94 % with a FiO<sub>2</sub> 1.0 on mechanical ventilation. Urine output following furosemide administration was 800ml. The patient was transferred to the Intensive Care Unit (ICU) for further management.

In the ICU, the patient was sedated and mechanically ventilated with a PEEP of 5 cm H<sub>2</sub>O and FiO<sub>2</sub> of 1.0. Arterial blood gas measurement obtained within an hour of the initial event showed a pH of 7.43, PaO<sub>2</sub> 57mmHg, PaCO<sub>2</sub> 36mmHG on a FiO<sub>2</sub> of 1.0. The blood pressure on inotropic support with adrenaline and dopamine (renal dose) infusion was 100mmHg with a heart rate of 120/min. A central venous line was inserted. Crystalloids were infused to maintain CVP between 8 to10 cm H<sub>2</sub>O. On auscultation, crepitations were confined to the bases of the lungs. ECG revealed sinus tachycardia. Chest radiograph showed bilateral pulmonary infiltrates suggestive of pulmonary edema with no cardiomegaly. A cardiology opinion was obtained to rule out a cardiac cause for pulmonary edema. CPK- MB was within normal limits and troponin- T test was negative.

With this treatment regime the patient showed considerable improvement. FiO<sub>2</sub> was gradually decreased over the next 6 hours to 0.3 to maintain SpO<sub>2</sub> >95%. Inotropic support was gradually reduced and finally discontinued by 18 h of the initial event. The vital signs were stable, lung fields were clear on auscultation, ABG analysis showed a normal profile with PaO<sub>2</sub> of 104 mmHg on a FiO<sub>2</sub> of 0.3. On the second day, neuromuscular block was discontinued. Ventilatory support (SIMV with pressure support) was gradually decreased over the next 48 h and the trachea was extubated on day 4 without further complications. The patient was discharged from the hospital on the ninth postoperative day.

### DISCUSSION

The number of patients with cancer who receive bleomycin is significant. These patients are at risk of developing acute respiratory distress syndrome postoperatively.<sup>4</sup> Because of lack of the bleomycin- inactivating enzyme, bleomycin hydrolase, in the lungs and the skin, bleomycin- induced toxicity occurs predominantly in these organs.<sup>5</sup> There are no pathognomonic signs or symptoms of bleomycin related pulmonary damage. In the preoperative evaluation of such patients, a history of dyspnea or dry cough, and the presence

of rales on physical examination are significant. Pulmonary function tests may be helpful in determining the extent of damage in known pulmonary fibrosis, but they are not predictive to subclinical disease.<sup>6</sup> Patients have also been found to be asymptomatic while developing physical findings, radiographic abnormalities, or pathologic findings suggesting toxicity. <sup>6</sup>

Several factors, including age, drug dose, route of administration, renal function, concomitant administration of oxygen, radiation therapy and a smoking history, may increase the risk of developing bleomycin drug toxicity.<sup>7</sup> The dose of bleomycin received cannot reliably be used to predict toxicity with some studies showing a significantly increased toxicity when the total dose exceeds 450 to 500mg<sup>8, 9, 10</sup> while it has not been dose related in others.<sup>11, 12</sup> The patient described here received a cumulative dose of 120 mg prior to surgery. In addition, he also received radiation therapy. Cisplatin associated renal toxicity can enhance bleomycin- induced pulmonary damage due to impaired elimination of the drug.<sup>13</sup> Our patient had received cisplatin but did not have any associated renal insufficiency as evidenced by normal renal function tests.

The association of oxygen and bleomycin induced pulmonary damage is not clear. Goldiner et al.<sup>4</sup> suggest that the FiO<sub>2</sub> during and after surgery should be kept as low as possible and that the fluid status should be aggressively monitored to avoid excessive crystalloid administration. These investigators postulated that bleomycin caused alveolar epithelial edema that progressed to necrosis of type 1 alveolar cells, fluid leakage into the alveolar space, and the formation of 'hyaline membranes' similar to that associated with oxygen toxicity. Goldiner et al.<sup>4</sup> believe that that this pathophysiologic similarity indicated a possible synergistic relationship between oxygen and bleomycin.

Contrary to the recommendations of Goldiner et al.,<sup>4</sup> several studies have questioned the need to limit FiO<sub>2</sub>.<sup>14, 15</sup> Donat and Levy,<sup>16</sup> in their study of 77 patients who received bleomycin, concluded that perioperative oxygen restriction is not necessary. The evidence from animal studies is also conflicting with some studies supporting the role of oxygen in potentiating bleomycin- induced injury<sup>17, 18</sup> and others refuting it.<sup>19, 20</sup>

Our patient, who had received bleomycin, was asymptomatic preoperatively. He received a FiO<sub>2</sub> of 0.3 for 2.5 h with normal oxygen saturation. Intraoperative fluid replacement with crystalloids was carefully administered to avoid fluid

overload. Colloids were not required because of limited blood loss. Serial postoperative ECGs , normal CPK- MB, negative troponin- T test, absence of cardiomegaly exclude a cardiac etiology of pulmonary edema. In addition, the patient also received cisplatin and radiation therapy, both identified as possible risk factors contributing to pulmonary toxicity.

To conclude, patients who have received antecedent bleomycin therapy are at increased risk for postoperative pulmonary complications. While there is much disagreement regarding the role of inspired oxygen concentration to be given perioperatively to these patients, it would be prudent to keep the inspired oxygen concentration at the lowest level providing adequate tissue oxygenation.

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