Bleomycin Induced Pulmonary Toxicity: A Case Report
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Citation

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. 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 100µg, and maintained with isoflurane in nitrous oxide and oxygen (FiO₂ 0.3) and incremental doses of morphine. Neuromuscular block was achieved with vecuronium and the lungs were ventilated to maintain Et CO₂ 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 SpO₂ 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
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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, Spo2 94 % with a FiO2
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 H2O and FiO2 of 1.0. Arterial
blood gas measurement obtained within an hour of the initial
event showed a pH of 7.43, PaO2 57mmHg, PaCO2
36mmHg on a FiO2 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 H2O. 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. FiO2 was gradually decreased over the next 6
hours to 0.3 to maintain SpO2 >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 PaO2 of 104 mmHg on a FiO2 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. Because of
lack of the bleomycin- inactivating enzyme, bleomycin
hydrolase, in the lungs and the skin, bleomycin- induced
toxicity occurs predominantly in these organs. 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. Patients have also been
found to be asymptomatic while developing physical
findings, radiographic abnormalities, or pathologic findings
suggesting toxicity.

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. 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
while it has not been dose related in others. While 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. 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. suggest that
the FiO2 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. believe that that this
pathophysiologic similarity indicated a possible synergistic
relationship between oxygen and bleomycin.

Contrary to the recommendations of Goldiner et al., several
studies have questioned the need to limit FiO2. Donat
and Levy, 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 and others
refuting it.

Our patient, who had received bleomycin, was asymptomatic
preoperatively. He received a FiO2 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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Support was from Institutional source

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