Journal of
Anesthesia & Intensive Care Medicine
ISSN: 2474-7653

Juniper Publishers
key to the Researchers

Case Report
Volume 3 Issue 2 –May 2017
DOI:10.19080/JAICM.2017.03.555607

J Anest & Inten Care Med

Bleomycin Lung Injury: A Case Report and Review of the Literature

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Submission: October 26, 2016; **Published:** June 09, 2017

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Abstract

Bleomycin is a drug used to in the treatment of Hodgkin's Lymphoma, amongst other tumours. Bleomycin has been implicated in causing pneumonitis and pulmonary fibrosis, now termed Bleomycin Lung Injury (BLI). BLI is a much debated subject, in terms of both its pathogenesis and management of patients after diagnosis.

In this paper, we reviewed the current knowledge of Bleomycin-Induced Lung Injury from a case report perspective. We will describe the case of a patient with BLI presenting to our ICU and discuss the available literature.

Keywords: Bleomycin; Acute Lung Injury, Chronic Lung Injury, Pneumonitis, Drug Toxicities, Free radicals

Abbreviations: BLI: Bleomycin Lung Injury; ARDS: Acute Respiratory Distress Syndrome; ICU: intensive care unit

Introduction

Bleomycin is a glycopeptide antibiotic, originally isolated from Streptomyces verticillus, and discovered to have anti-tumour cytotoxic activity in 1966 [1]. It is now commonly used as a chemotherapeutic agent for germ cell tumours, lymphoma, squamous cell tumours of the head, neck and axilla, Kaposi's sarcoma and cervical cancer. However, Bleomycin has also been associated with pulmonary toxicity, causing in some cases pneumonitis, pulmonary fibrosis, and fatal acute respiratory distress syndrome (ARDS) [2-4]. Lung damage associated with Bleomycin is termed Bleomycin Lung Injury (BLI).

In 1990 it was estimated that approximately 10% patients who have treatment with Bleomycin develop some form of lung injury, with 1% developing fatal pulmonary fibrosis [5]. However, since then, incidences of lung injury of between 0 and 46% of all patients who take the drug had been reported [6]. Mortality rates range between 2 and 10% of those affected, although some studies report up to 27% mortality, and in mechanically ventilated patients mortality rates of up to 33% have been reported [2,6-8].

There has been put forward a suggestion that oxygen therapy following Bleomycin exposure potentiates lung damage [9-11]. This is due to the supposed mechanism of action of Bleomycin involving oxygen-free radicals, combined with a number of studies on animals indicating an association.

Other drugs may also exacerbate or protect against this unwanted side effect. [12]. For this reason, the management of a patient following Bleomycin therapy, whether presenting with or without symptoms of lung damage, is crucial.

It is important to note that patients treated with Bleomycin are immunosuppressed, and hence more likely to develop various infections. Bacterial, viral and fungal infections will all produce lung injury and have similar clinical presentations to BLI, i.e. hypoxia. These infections are more common than Bleomycin Lung Injury and, in these circumstances, lack of oxygen as part of the sepsis syndrome increases mortality and should be treated promptly. Hence, when treating these patients infectious causes of hypoxia/lung injury should be considered and treated first.

The benefits versus the risks of oxygen therapy should be considered on an individual patient basis, depending on the index of suspicion of BLI (presence or absence of an alternative cause), Bleomycin dose and time since last dose and the presence of other risk factors.

The following is a case report of a patient admitted to the intensive care unit (ICU) with ARDS following chemotherapy with Bleomycin.

Case Presentation

A 39 year-old man presented to the Accident and Emergency Department complaining of shortness of breath. He had a known history of Hodgkin's Lymphoma for which he had been treated with 5½ cycles of ABVD chemotherapy (Doxorubicin, Vinblastine, Bleomycin and Dacarbazine), including 17.500 units of Bleomycin per cycle. His last cycle had finished 10 days before the acute episode of shortness of breath.=

He also had known pulmonary hypertension and had a pericardial effusion that required drainage three months before this presentation. He had had multiple pulmonary emboli and was previously noted on echocardiogram to have a dilated right heart. The patient had no other notable medical history except that of smoking tobacco, cannabis and heroin, and previous history of intravenous drug use.

On admission the patient was alert and conscious, pulse was 124 beats per minute, temperature 36.2 ºC, respiratory rate was 28 breaths per minute, and oxygen saturation was 94% on air. He was noted to have a Skin Tunnelled Central Venous Catheter (Hickman®) in situ, and on examination of his chest bibasal crepitations. Initial differential diagnosis was that of pneumonia, pulmonary oedema (in light of his known cardiac pathology), or pulmonary embolism (in light of his relevant history).

Chest X-ray showed bibasal infiltrates. He was started on empirical antibiotic treatment with Co-amoxiclav and Clarithromycin. Investigations found a high white blood cell count but there was no growth on blood or sputum cultures, and the patient remained apyrexial.

Four days after admission to hospital he was admitted to the Intensive Care Unit (ICU) with progressive respiratory failure and hypoxia. An initial target of paO2 of 7kPa was set and, due to his background of exposure to Bleomycin, when he failed to respond to low flow oxygen at 40% FiO2 he was started on steroids at a dose of 1 mg/kg of Prednisolone (later tapered down by 10 mg every third day), and received an early trial non-invasive bi-level positive airway pressure (BIPAP®) ventilation. His oxygen saturation target was set at 82 - 85% corresponding to a PaO2 of 7-7.5 kPa as he had initially a single organ failure with no signs of systemic sepsis, rather than the recommended SaO2 of 88-92% (i.e. PaO2 8-8.5) [13]. This was a difficult clinical decision made after taking into consideration the patient's previous history of Bleomycin therapy and the deleterious effects oxygen has in lungs previously exposed to this drug, as we will discuss later. The possibility of an already existent Bleomycin Induced Lung Injury causing the current respiratory failure was also considered. The risk/benefit balance between permissive hypoxia versus the potential toxic effects predisposed by Bleomycin was carefully considered. Unfortunately, there is no suggestion from the literature as to what is the optimal saturation target in this patients. The patient did not have any other concomitant organ failures and he was carefully monitored for any signs of developing end organ hypoxia (acidosis, hyperlactatemia…). It was worsening hypoxemia that led to intubation and ventilation and not other organ dysfunctions.

In spite of this, the patient continued to deteriorate, requiring intubation and mechanical ventilation 24 hours after admission to the ICU. Decision was made to limit his inspired oxygen fraction in light of his Bleomycin exposure. With the above PaO2 as a target, he was ventilated using a lung protective strategy, initially 6 ml per kilogram of IBW (Ideal Body Weight), pressure controlled ventilation with a 10 cmH2O PEEP level, thus limiting the plateau pressure at 30 cmH2O and was started on nitric oxide at 10-15 ppm; with FiO2 limited to 0.4 immediately following intubation.

Broncho-alveolar lavage was performed, but the microbiological samples were negative for all the respiratory viruses including CMV, and showed no bacterial or fungal growth. Pneumocystis jiroveci and Aspergillus antigen were also negative. An echocardiographic study did not show significant changes with respect to previous studies.

CT chest appearance was recognised (by method of exclusion) as that of a drug-induced lung injury. Opinion from respiratory specialists agreed BLI as the most likely cause of lung injury.

Over the following four days his respiratory failure deteriorated further and he progressed into multi-organ failure requiring vasopressor and inotropic support. On the 5th day after admission to ICU his lung injury worsened with no response to any treatment. After consulting his family treatment was withdrawn and he was kept comfortable.

Discussion

This patient's history of exposure, the clinical progression, the absence of any other alternative diagnosis along with the CT appearances makes Bleomycin-induced Lung Injury the most likely diagnosis in this case. In view of the index of suspicion and the potential harm due to oxygen therapy this patient was managed differently from other patients with ARDS in the ICU, particularly regarding oxygen therapy.

Bleomycin exerts its cytotoxic effects by induction of free radicals. Bleomycin forms a complex with Fe (II), which is oxidized to Fe (III). This causes reduction of oxygen to free radicals, which causes single and double-strand breaks in cellular DNA leading to genomic instability of damaged cells. It also inhibits tumour angiogenesis [2,14,15].

Bleomycin causes an increase in reactive oxygen species resulting in oxidative stress and pulmonary fibrosis. It has been found to induce apoptosis and senescence in lung cells [6]. It has also been suggested that Bleomycin induces oxygen sensitivity,

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and in animal studies oxygen has been shown to augment lung injury from Bleomycin exposure [13-17]. Previous studies cited.

Bleomycin-induced synthesis of pro-collagen by fibroblasts as one of the key mechanisms of action of Bleomycin-induced fibrosis, however recent data indicate the role of pro-inflammatory cytokines IL-18 and IL-1 beta, as well as scaffold proteins such as caveolin-1 as more important in the mechanism of injury [14-18]. This is then followed by collagen deposition by fibroblasts, which are both directly and indirectly stimulated by Bleomycin itself [19]. Bleomycin is broken down by an enzyme found in most tissues called Bleomycin Hydrolase [5,20].

This enzyme has been shown to be involved in post-proteasomal processing of peptides for antigen presentation; the proteasome generates some precursor peptides which are extended at their N-termini with the exact ligands for presentation on MHC class I molecules [21,22]. It is thought that relative lack of this enzyme in lungs and skin causes Bleomycin to accumulate in these organs, causing toxicity [6,20,23]. This higher concentration of drug in the lungs, combined with the high availability of oxygen, may contribute to the propensity of the lungs to Bleomycin-induced damage [6,21].

Among patients who have Bleomycin pulmonary toxicity there appears to be three distinct reactions. The normal clinical manifestation of Interstitial Pneumonia occurs weeks to months after initiation of chemotherapeutic treatment; however a hypersensitivity reaction and a delayed response reaction have both been described. The hypersensitivity reaction was termed such in light of lung biopsy results and the pathologic appearance, whereas delayed onset reaction has occurred between two and ten years after initiation of treatment [23-25]. These distinctions are clinically important because of the response of the pneumonitis to steroids: the Hypersensitivity Pneumonitis having a markedly favourable response to corticosteroids, compared to the Interstitial Pneumonitis, with a non-hypersensitive pathogenesis, for which response to steroids is variable [2,25,26].

There are number of recognised risk factors for developing lung injury in response to Bleomycin. The most commonly described in the literature are dose, age, route of administration, kidney function, and a history of smoking [27].

Cumulative dose of over 450mg was identified as an independent risk factor for BLI27. In patients treated with Bleomycin at doses lower than 450mg there was a 3to5% incidence of BLI. This is increased by 13% with doses of 450-549 mg and by 17% with more than 550mg [27,28]. However, BLI has been described in patients even with low doses of Bleomycin, and fatalities have been reported amongst them [29,30].

Patients over the age of 70 years were found to be at higher risk of BLI, however this may be confounded by the decrease in kidney function with advancing age [2,27,31,32].

Route of administration has been looked at as a risk factor, and found that intravenous bolus was more likely to induce injury than continuous intravenous infusions [33,34].

Reduced kidney function is another factor likely to increase the risk of BLI [2,27]. One study found creatinine clearance to be the most important risk factor for decrease in lung function by a particular method of monitoring.

Cisplatin, a nephrotoxic agent, has been extensively studied as a synergistic factor in the production of BLI [35-38]. As well as other drugs such as the granulocyte colony-stimulating factor (G-CSF) [39,40].

A history of smoking has also been shown to increase the risk of BLI [2,22,27] Lower et al; showed radiographic alterations suggestive of BLI in 55% of patients receiving Bleomycin who were smokers, compared with 0% of the non-smokers, while animal studies have shown that cigarette smoke potentiates the deleterious effect of Bleomycin on the lungs [41,42].

Some drugs have been found to minimise lung injury induced by Bleomycin. In older literature, studies on animals showed soluble Fas antigen, IL-1–receptor antagonists, Keratinocyte Growth Factor, Cyclosporin, antibodies against TNF-CD3 receptor, Dexrazoxane and Amifostine to be effective.[2] Dexrazoxane and Amifostine block Bleomycin-induced free radicals [2]. More recent animal studies have shown N-acetylcysteine combined with Dexrazoxane to be effective as an antioxidant therapy, as well as PG-490-88, a water-soluble derivative of Triptolide, and Dimethyl-Prostaglandin E2. However, evidence from human studies is not readily available in the literature [43-45].

Because of the mechanism of Bleomycin involving oxygen-free radicals, the association between BLI and oxygen therapy has been studied. In animal studies oxygen was found to potentiate the effects of Bleomycin induced Lung Injury. [8,9,11,17]. It is generally accepted that high levels of FiO2 should be avoided in patients with previous exposure to Bleomycin, although the restriction of oxygen therapy intra and perioperatively has been debated [46,47].

Interestingly, nitric oxide has been shown to improve lung architecture and pulmonary hypertension in animals; however the evidence base in humans is limited [48].

Conclusion

Bleomycin is an effective chemotherapeutic drug for a number of different tumours, including Hodgkin's lymphoma. Because of its efficacy and because of the relatively low incidence of lung injury, it is not feasible to discontinue its use, even in the face of a guaranteed number of fatalities as a result of BLI.

What is important for patients who are exposed to Bleomycin is how they are managed after initiation of chemotherapy treatment. Firstly, monitoring of lung function and lung appearance on radiography is important. A high index

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of clinical suspicion is crucial in any patient who has undergone a treatment regimen including Bleomycin presenting with respiratory symptoms. Identifying patients with other risk factors such as old age, renal failure, smoking history and skin toxicity; and careful follow up is essential. While maintaining said index of suspicion, investigating for and treating other more common causes of hypoxia in immunosuppressed patients, such as bacterial, fungal or viral infections; is essential.

Patients exposed to Bleomycin and presenting with severe respiratory failure represent a unique scenario in Critical Care where we need to tightly control oxygen delivery to maintain the minimal acceptable tissue oxygenation that allows survival and functionality at a cellular level, as opposed to trying to maximise it.

Until further evidence surrounding Bleomycin and oxygen therapy is produced, in patients requiring oxygen therapy a careful evaluation of risks and benefits should be undertaken and decisions should be made on an individual case-by-case basis. Early input from oncologists, radiologists, respiratory physicians and critical care physicians is essential in this decision-making process.

Further research into drugs attenuating BLI may aid prognosis of future patients, however the single most important thing remains to expand the currently limited evidence base on Bleomycin Lung Injury, and formally follow up all patients who are treated with this drug.

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