Bleomycin Overdose in a Patient with Stage II Hodgkin Lymphoma: A Case Report of a Medication Error

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October 28, 2022

Abstract

Bleomycin is an antibiotic with cytotoxic properties, commonly used in combination regimens for the treatment of Hodgkin lymphoma. The inconsistency in dosage nomenclature of bleomycin seems to be universal in many countries, which increases the risk of medication error. However, as far as we know no cases have reported. Here we present a case report of a medication error caused by bleomycin overdose. A 25-year-old patient with Stage II Hodgkin Lymphoma received a 150 USP bleomycin, which dosage was ten times higher than usually used, as part of the doxorubicin, bleomycin, vindesine, dacarbazine protocol (ABVD) at the third cycles of chemotherapy. After the medication error was found, the patient was immediately treated with intravenous rehydration and furosemide to promote clearance of drugs. To prevent lung injury, the methylprednisone and acetylcysteine was given. The patient developed a slight nausea and a mild rash, which gradually improved after the treatment. After the evaluation with PET-CT, the patient received four cycles of AVD chemotherapy. During the treatment and one-year follow-up period, no other obvious abnormalities were observed. The toxicities, clinical managements and selection of further chemotherapy after bleomycin overdose deserved serious attention in this case. More importantly, the management measures after this error can be used for reference in other hospitals.

Full Title:

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Running Title:

A Case Report of Bleomycin Overdose

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Abstract

Bleomycin is an antibiotic with cytotoxic properties, commonly used in combination regimens for the treatment of Hodgkin lymphoma. The inconsistency in dosage nomenclature of bleomycin seems to be universal in many countries, which increases the risk of medication error. However, as far as we know no cases have reported. Here we present a case report of a medication error caused by bleomycin overdose. A 25-year-old patient with Stage II Hodgkin Lymphoma received a 150 USP bleomycin, which dosage was ten times higher than usually used, as part of the doxorubicin, bleomycin, vindesine, dacarbazine protocol (ABVD) at the third cycles of chemotherapy. After the medication error was found, the patient was immediately treated with intravenous rehydration and furosemide to promote clearance of drugs. To prevent lung injury, the methylprednisone and acetylcysteine was given. The patient developed a slight nausea and a mild rash, which gradually improved after the treatment. After the evaluation with PET-CT, the patient received four cycles of AVD chemotherapy. During the treatment and one-year follow-up period, no other obvious abnormalities were observed. The toxicities, clinical managements and selection of further chemotherapy after bleomycin overdose deserved serious attention in this case. More importantly, the management measures after this error can be used for reference in other hospitals.

Key words

Bleomycin, overdose, Hodgkin lymphoma, medication error, case report

Introduction

Bleomycin is an antibiotic with cytotoxic properties, commonly used in combination regimens for the treatment of Hodgkin's and non-Hodgkin's lymphoma. In addition to its antitumor activity, bleomycin is used as a sclerosant in the treatment of vascular malformations and in recurrent malignant pleural effusions (1). Bleomycin is mixtures included bleomycin A2, B2 and A5. Published protocols give bleomycin doses in milligrams (mg), international units (IU), or United States Pharmacopoeia units (USP units). Even though *Jim Siderov* has noted that dosage nomenclature of bleomycin need to be standardised to avoid errors in 2001 (2), the inconsistency in nomenclature seems to be universal in many countries including China. This inconsistency increases the risk of medication error. However, as far as we know no cases have reported. Here we present a case report of accidental bleomycin overdose with injection of bleomycin 150 USP (equivalent to ten times the common dose) as part of the doxorubicin, bleomycin, vindesine, dacarbazine protocol (ABVD). We present the following article in accordance with the CARE reporting checklist.

Case presentation

Chief complaints

A 25-year-old man presented with mediastina mass for two months in physical examination.

History of present and past illness

The patent was diagnosed with classical Hodgkin's lymphoma (II A) in*December 2019* . He had completed two cycles of ABVD chemotherapy (doxorubicin 80 mg, bleomycin 15 USP, vindesine 4 mg and dacarbazine 700 mg). In *February 11, 2020* , the patient was admitted to our hospital for further chemotherapy.

Personal and family history

The patient denied any other relevant personal or family history.

Physical examination

Initial vital signs were as follows: blood pressure, 120/60 mmHg; heart rate, 82 beats/min; respiratory rate, 21/min; body temperature, 36.4 °C. The general condition of the patient is good, and the *KarnofskyPerformance Score* (KPS) was 90. Bilateral cervical, axillary and inguinal lymph nodes were palpable.

Laboratory examinations

The immunohistochemistry results of mediastina mass in *December 2019* showed CD15 +, CD30 +, CD3 -, LCA -, CD20 +, PLAP -, PAX-5 + (weak), TDT -, CD5 -, Ki-67 (60 %). The lab values of routine blood, urine, and stool tests were within normal range.

Imaging examinations

The PET-CT results in *December 2019* showed multiple hypermetabolic active lesions were observed in the region of the thymus gland of anterior superior mediastinum, the root of the left neck and the the left clavicular fossa. Color doppler ultrasound indicated bilateral cervical, bilateral axillary and bilateral inguinal lymphadenopathy. A computed tomography (CT) scan showed visible nodal mass of 51 × 22 cm in the anterior superior mediastinum.

Final diagnosis

Based on the above findings, a diagnosis of classical Hodgkin's lymphoma (II A) was established.

Treatment

In *12 & 19 February 2020* , the patient received the third cycles of ABVD chemotherapy. However, the doctor gave the wrong dose (150 USP, equivalent to ten times the common dose) of bleomycin and the time of medication error was at 14:54 in *19 February 2020* . The rest of the drugs were administered in the same doses as previously performed.

The medication error was found at 13:00 in *20 February 2020.* The patient was immediately treated with intravenous rehydration (3000 ml/m^2) and furosemide 20 mg to promote clearance of drugs. Then to prevent lung injury, the methylprednisone was given 40 mg qd via intravenous route for three days, which changed to 8 mg qd orally for nine days and decreased to 4 mg qd orally for nine days. The acetylcysteine solution for inhalation BID was administered for 12 days, and the acetylcysteine tablets 0.6 g TID were used orally for 21 days. At the same time, the pulmonary function test showed the lung function of the patient was normal. No obvious abnormalities were detected by the thoracoabdominopelvic CT scan and echocardiography. All lab values were within normal range except for a decreased lymphocyte count of 0.87×10^9/L (LYMPH, reference range, 1.10×10^9 to 3.20×10^9/L) and an elevated C-reactive protein level of 17.44 mg/L (CRP, reference range, 0 to 5 mg/L).

Outcome and follow-up

Subsequently, the patient was observed in intensive care unit for one month. From *February 21* to *February 23* , the patient developed a slight nausea, which resolved after the injection 40 mg of esomeprazole. Then the patient developed a mild rash in *February 29* , which gradually improved after the given of compound polymyxin B ointment. PET-CT results in *March 9* revealed that the patient was in lymphoma remission and the PET 5-point scale (Deauville criteria) was 2. Then the patient received four cycles of AVD chemotherapy (doxorubicin 80 mg, vindesine 4 mg and dacarbazine 700 mg). During the treatment and one-year follow-up period, the function of lung, liver, kidney and heart in this patient was basically normal. The timeline of the patient's management and outcome is presented in *Figure 1* .

Ethical statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal (as shown in the *Supporting Information*).

Discussion

This case report describes accidental bleomycin overdose caused by human error and failure of the system to block the chain of events. The toxicities and clinical management after medication error will be discussed, and a detailed analysis of the chain of events that resulted in the incident will be provided.

After injection, bleomycin is widely distributed throughout the body. Then the bleomycin is inactivated by a cytosolic cysteine proteinase enzyme, bleomycin hydrolase. The enzyme is widely distributed in normal tissues with the exception of the skin and lungs, both targets of bleomycin toxicity (3). Thus, we focused closely on the pulmonary and skin toxicities. According to the instruction, the pulmonary toxicity occurs in approximately 10 % of treated patients and is both dose and age related, being more common in patients over 70 years of age and in those receiving over 400 units total dose. Published articles have shown that the incidence of severe lung toxicity was 0-2 % in the patients exposured to a total dose [?] 270 USP, the incidence increased to 6-18 % in the patients exposured to a total dose [?] 360 USP (4-6). In this case, a total dose of bleomycin the patient received was 225 USP due to the medication error. However, we did not observe any pulmonary toxicity during one-year follow-up. The possible reasons are shown as follows: (1) multiple measures were used to protect bleomycin-induced toxicity; (2) the total dose of bleomycin that the patient received was less than 270 USP; (3) the patient was young man aged 25 years, thus the incidence of lung injury was relatively low. Based on the instruction (3), the skin toxicity is a relatively late manifestation usually developing after 150 to 200 USP of bleomycin have been administered and is also related to the cumulative dose. This is consistent with our case that the patient developed a mild rash 10 days after the medication error when the cumulative dose of bleomycin reached 225 USP.

Bleomycin has a renal metabolism with 50 % of dose eliminated in four hours after its administration and 70 % in the next 24 h (7). For this case, the time between the administration of the bleomycin and the detection of the medication error was 22 h. Even though most of the bleomycin had been cleared from the body, intravenous rehydration (3000 ml/m^2) combined furosemide 20 mg were used to promote clearance of remaining medication. As the most serious side effects of bleomycin are pulmonary adverse reactions and the most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis, we undertook several approaches to protect the pulmonary toxicity. Up to now, there are no proven efficient to prevent the bleomycin-induced lung injury in humans. Oxidative stress has been implicated as an important factor in the development of bleomycin-induced pulmonary toxicity. A lot of non-clinical studies have reported that N-acetylcysteine amide, a thiol antioxidant, could prevent and ameliorate bleomycin-induced toxicity in human alveolar basal epithelial cells (8, 9). Therefore, the N-acetylcysteine amid was administered via inhalation and intravenous route. In addition, corticosteroids are widely considered to be the standard therapy in symptomatic patients with bleomycin-induced lung injury (10). The dosage of corticosteroids was initially 0.75-1 mg/ (kg*d) of prednison, which was gradually decreased according to the condition of the patients (11). Thus, the equipotent dose of methylprednisone (40 mg) was given initially, and gradually decreased to 4 mg. Luckily, no serious adverse events were observed during the treatment and one-year follow-up period.

Due to the medication error, how the next cycle of chemotherapy was chosen was a matter of further exploration. The medication error occurred in the third cycle of chemotherapy. According to the*RAPID* (12), *CALGB 50604* (13), and *RATHL* (14) study, PET-CT scan should be performed after 3 cycles of ABVD in patients with newly diagnosed, nonbulky stage I or II Hodgkin lymphoma. The PET 5-point scale (Deauville criteria) of this patient was 2. The further chemotherapy should be one-two cycles of ABVD or four cycles of AVD (12-14). Finally, we choose the four cycles of AVD chemotherapy for the following two reasons. First, the pulmonary toxicity of bleomycin is dose related. Second, the omission of bleomycin from the ABVD regimen after negative findings on interim PET resulted in a lower incidence of pulmonary toxic effects than with continued ABVD but not significantly lower efficacy (14).

The chain of events was initiated by incorrect drug prescription. The doctor explained the error was likely caused by reduced concentration during a routine task combined with the inconsistency in nomenclature of bleomycin. Historically, bleomycin dosage has been described in terms of milligram potency (mg potency), in which 1 mg potency corresponded to 1 unit. In the original preparations 1 mg potency was also equivalent to 1 mg by weight (mg weight). Modifications and improvements in purification over time have meant that ampoules labelled as containing 15 mg—that is, 15 units—contained less than 15 mg weight of bleomycin. In 1995 labelling of bleomycin products in Australia changed from USP units to IU in line with changes in the *British Pharmacopoeia and European Pharmacopoeia* . The 10 mg vial, formerly labelled as containing

15 USP units, is now labelled as containing 15 000 IU. Therefore, 1.5-2 USP units is equivalent to 1500 IU, which is equivalent to 1 mg (by weight) or approximately 1.5 mg (by potency) (2). Furthermore, the nurses and pharmacists failed to discover the medication error.

In order not to repeat similar medical errors, the following measures were taken in our institution. Firstly, we optimized the hospital information system of prescription pre-checking to intercept the drug overdose. Secondly, lecture series about medication safety of bleomycin were held for doctors, nurses and pharmacists. On top of that, we call the attention to the consistency in nomenclature of bleomycin to prevent wrong-route administration incidents.

Conclusion

This case report a medication error of bleomycin overdose, and the toxicities, clinical managements and selection of further chemotherapy after bleomycin overdose in our case can be referred by others. More importantly, the management measures after this error can be used for reference in other hospitals.

Acknowledgments

This work was supported by the Natural Science Foundation of Shan Dong [No. ZR2022QH119] and the Medical Research Guidance Plan of Qingdao Municipal Health Committee [No. 2019-WJZD063, 2021-WJZD091].

Conflicts of interest statement

None

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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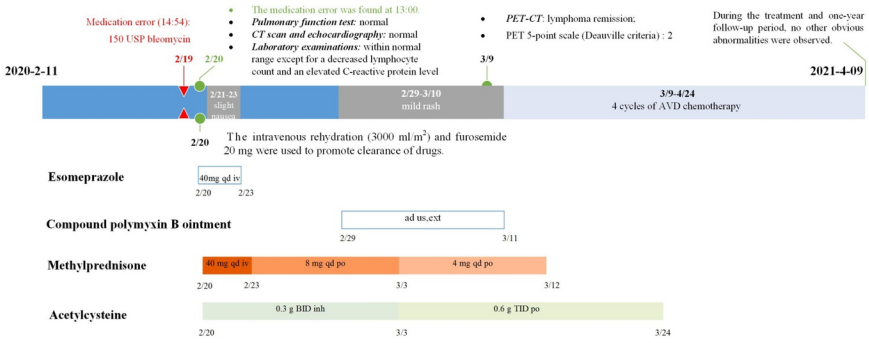
Figure 1 Schematic historical and current information from the episode of care



Supporting Information

Additional supporting information can be found online in the Supporting Information section at the end of this article.