Case report

Hypersensitivity Induced by Intravenous Etoposide-A Case Report

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Abstract

Etoposide (VP-16) exerts its anticancer effects by inhibiting the enzyme, topoisomerase II. This ultimately leads to unrepaired breaks in cellular DNA. The U.S. Food and Drug Administration (FDA) approved etoposide for treatment of small cell lung cancer and refractory testicular cancer. It also has been used to treat acute lymphoid leukemia, acute myeloid leukemia, Hodgkin’s and non-Hodgkin’s lymphoma. Common side effects include bone marrow suppression, alopecia, and gastrointestinal symptoms. Hypersensitive reactions to etoposide are uncommon and the underlying mechanism is unclear. A 71-year-old man with adenocarcinoma lung cancer experienced acute dyspnea, chest tightness, mild hypertension and hypoxia minutes after starting an infusion of etoposide. The infusion was stopped immediately, pharmacologic agents were administered and the symptoms of hypersensitivity were resolved. Subsequently, the patient was given paclitaxel without incident. Chiang Mai Medical Journal 2011;50(3):89-93.

Keywords: etoposide, hypersensitivity

Etoposide has been used in the treatment of various malignant conditions for over 30 years. Similar to all other drugs, this one can induced hypersensitive reactions. The literature in Thailand reported a case of intravenous etoposide hypersensitivity in a patient with extragonadal germ cell tumor. This case was rechallenged successfully with an oral form of etoposide. Intravenous etoposide is well tolerated in general. Most reported allergic reactions caused by anticancer agents are of the type I category, which
occurs immediately and for usually less than 30 minutes after contact with the drug.\(^2\)

Type I hypersensitivity reaction manifests from dyspnoea, chest discomfort, hypotension, bronchospasm and/or skin flushing.\(^1\)

It remains unclear in intravenous etoposide whether hypersensitive reaction is related to the active drug or solvent.\(^1\)

This report gives details of a male patient with adenocarcinoma lung cancer. Despite experiencing hypersensitive reaction to intravenous etoposide, he successfully tolerated a new regimen without any allergic reaction.

**CASE REPORT**

A 71-year-old man, with adenocarcinoma lung cancer (T\(_4\)N\(_2\)M\(_0\))-stage IIIB, visited Maharaj Nakorn Chiang Mai University. This case report was approved by the Ethics Committee at the Faculty of Medicine, Chiang Mai University, Thailand. The patient received a standard regimen (cycle 1) consisting of carboplatin AUC 5 (Day 1) and 100 mg/m\(^2\) of intravenous etoposide (Days 1-3). Laboratory values before treatment were a white blood cell count of 10.5x10\(^3\)/mm\(^3\), hemoglobin of 12.0 g/dL, hematocrit of 35.0\%, platelet at 507x10\(^3\) and serum creatinine of 0.8 mg/mL. The patient was premedicated intravenously with 10 mg of dexamethasone and 10 mg of metoclopramide before chemotherapy to prevent nausea and vomiting.

The regimen to be used for this case was adapted from Albain et al.,\(^4\) with carboplatin and etoposide infused on day 1 and days 1-3, respectively. Thirty minutes after premedication, administration of 400 mg of carboplatin (AUC5) in 100 mL of D5W was started and lasted for over one hour. Afterwards, 150 mg of etoposide in 500 mg (100 mg/m\(^2\)) of 0.9\% sodium chloride was meant to be given for over 4 hours. However, within five minutes the patient developed acute dyspnea, chest tightness, mild hypertension (140/90 mmHg) and oxygen saturation that was 94\% at room air. Physical examination showed bronchospasm of the bilateral lungs. The etoposide infusion was stopped immediately, and 10 mg of dexamethasone, 10 mg of chlorpheniramine and, 50 mg/2 mL of ranitidine hydrochloride were administered intravenously, as well as nebulizer berodual forte and oxygen via the nasal cannula being given. The symptoms were resolved completely within 5 minutes.

After the hypersensitivity from etoposide, the regimen was changed to the protocol of Belani et al.,\(^5\) This regimen comprised paclitaxel (200 mg/m\(^2\)) and carboplatin (AUC6) on day 1. In cycle 1 on day 3, the patient was given 300 mg of paclitaxel in 250 mg of 0.9\% sodium chloride successfully for 3 hours. After the first cycle of Caboplatin/Paclitaxel, the patient received concurrent chemoradiation with six cycles of weekly Carboplatin (AUC=2)/Paclitaxel (50 mg/m\(^2\)). The treatment was completed with one cycle of consolidation Carboplatin/Paclitaxel, after which the patient’s CT showed partial regression of lung mass. Then the patient was followed up for surveillance.

**DISCUSSION**

The rare toxicity of etoposide is a type I hypersensitive reaction, demonstrated by dyspnoea, chest discomfort, hypotension, bronchospasm and/or skin flushing.\(^2\)

Hypersensitive reactions to etoposide are
Hypersensitivity induced by intravenous etoposide

reported infrequently (1-3%).\(^{(1,6)}\) In most patients, reactions arise within 10 minutes and are resolved by discontinuing infusion and administering pharmacologic agents. The patient in this case reported acute dyspnea and bronchospasm within 5 minutes of starting the infusion. Hypersensitive reactions are described following Coombs and Gell’s classification, which uses 4 types (I-IV).\(^{(7)}\) These types depend on a mechanism; either antibody-mediated (type I to III) or T cell mediated (type IV). Type I reactions usually occur immediately after administration and are antibody mediated. In this reported case, it was believed that the patient experienced a type I hypersensitive reaction in addition to releasing vasoactive substances such as histamine, which resulted in acute symptoms. The exact mechanism behind these reactions to etoposide is unknown. A report from Thailand by Sookprasert \textit{et al},\(^{(3)}\) found that hypersensitivity from intravenous etoposide can be rechallenged with an oral form of the drug. Bernstein \textit{et al},\(^{(8)}\) reported drug concentration and rate of infusion in both etoposide (active drug) and its solvent, polysorbate 80 (Tween 80), which are suspected of causing hypersensitive reactions. This case report used polysorbate 80 as a solvent of etoposide. There have been few reports of anaphylaxis reactions to etoposide.\(^{(9,10)}\) Therefore, a case report from Taguchi \textit{et al},\(^{(9)}\) found that a patient with ovarian choriocarcinoma, who was treated with additional chemotherapy and planned to use the combined regimen of etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine, showed anaphylactic symptoms after 2 min of etoposide administration. In this case, etoposide concentration was diluted to 50%, and the drug administration rate reduced by half. With this modified regimen, the patient showed no anaphylaxis symptoms. Collier \textit{et al},\(^{(11)}\) succeeded in using etoposide phosphate in patients with previous etoposide hypersensitivity. In this case, the regimen of chemotherapy was changed, and this succeeded in completing the cycle of chemotherapy with no hypersensitivity. However, another possible alternative is the use of oral instead of intravenous etoposide, due to a lower incidence of hypersensitivity in oral etoposide when compared to the intravenous one.

CONCLUSION

The hypersensitivity of etoposide occurs infrequently, but it can be life threatening. The patient care team should be aware of this possible complication when it uses this drug in the treatment regimen.

REFERENCES


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บทคัดย่อ
อีโทโปซายเป็นยาเคมีบำบัด มีฤทธิ์ยับยั้งเอนไซม์โทโพไอโซเมอเรสชนิดที่สอง ทำลายระบบ DNA คณะกรรมการอาหารและยาของประเทศสหรัฐอเมริกาอนุมัติให้ใช้อีโทโปซายในทุกการรักษาโรคมะเร็ง ชนิดต่างๆได้แก่ acute lymphoid leukemia, acute myeloid leukemia, Hodgkin’s และ non-Hodgkin’s lymphoma อาการข้างเคียงที่พบบ่อยคือการกระตุ้นประสาท ปวดริม และผลต่อหัวใจ อัตราการแพ้ยาอีโทโปซายมีอยู่แต่ไม่ทราบกลไกที่แน่นอน รายงานนี้เป็นรายงานในผู้ป่วยชายไทยอายุ 71 ปี เป็นมะเร็งปอด มีอาการเหนื่อยฉับพลัน แน่นหน้าอก ความดันเลือดสูงเล็กน้อย และมีภาวะพรองออกซิเจน จึงหยุดยาอีโทโปซายทันทีและรักษาอาการแพ้ยาที่เกิดขึ้น หลังจากนั้นจึงเปลี่ยนสูตรยาเป็น paclitaxel แทน โดยไม่ปรากฏปัญหาอีก วิชัยวัฒนธรรม 2554:50(3):89-93.

คำสำคัญ: อีโทโปซาย ภาวะแพ้ยา