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Hypersensitivity reactions to etoposide phosphate

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Abstract

Etoposide phosphate is a prodrug of intravenous etoposide recommended for use in patients with demonstrated allergy to etoposide. We have previously published a case series comprising six patients who were successfully treated with etoposide phosphate following preceding etoposide hypersensitivity. In this new paper we now present the cases of two patients who had allergic reactions to both etoposide and etoposide phosphate. As such, we suggest that whilst most patients with etoposide hypersensitivity can safely be treated with etoposide phosphate, a small number are at risk of an additional allergic reaction to etoposide phosphate. Patients being treated for the first time with etoposide phosphate after etoposide allergy should receive their first dose under medical supervision.

Keywords

Hypersensitivity, allergy, etoposide phosphate, germ cell tumour

Introduction

Etoposide is a widely used topoisomerase II inhibitor with demonstrated efficacy against a broad spectrum of malignancies. The use of etoposide is central to the curative chemotherapy treatment of testicular cancer and high-risk gestational trophoblastic disease where it forms part of the BEP and EMA-CO regimens.^{1,2}

The administration of etoposide is on occasion associated with hypersensitivity reactions that occur in around 1% of cases.³ Patients may experience fevers, chills, urticaria, dyspnoea and bronchospasm.^{4,5} The mechanism underlying this hypersensitivity reaction is unclear; one theory postulates that the reaction is due to the solvent in which the drug is diluted.⁶ In support of this is the fact that there have been no documented allergic reactions to oral etoposide, which does not contain the same polysorbate solvent as intravenous etoposide. Furthermore, the experimental administration of

the polysorbate solvent itself has been shown to stimulate hypotension, tachycardia and histamine release in experimental animals.⁷

Etoposide phosphate (Etopophos) is an intravenous etoposide prodrug that is rapidly and completely converted to etoposide by (hepatic) alkaline phosphatase enzymes.⁸ Etopophos does not contain the polysorbate excipient used in intravenous etoposide. It has previously been thought to not carry a risk of hypersensitivity reaction and has been considered a safe alternative in patients who have previously experienced an allergic reaction to etoposide. A number of case reports and our own case series have highlighted the safety of Etopophos in patients with preceding etoposide allergy.^{3,6,9,10}

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However, there has recently been one case published in which a patient experienced an anaphylactic reaction to Etopophos.¹¹ In this case, a 14-month-old girl was treated with etoposide for acute myeloid leukaemia and tolerated the first five doses without any complications. On administration of subsequent doses of etoposide, however, she experienced a hypersensitivity reaction characterised by erythema, urticaria and tachycardia. The decision was therefore made to substitute Etopophos for etoposide. An infusion of only 9.4 ml unfortunately resulted in the patient becoming flaccid, hypotensive and unresponsive and she required aggressive resuscitation.

In this report, we present two further cases of adult patients developing hypersensitivity reactions to Etopophos after it was used as an alternative when an allergic response to etoposide occurred.

Case 1

A 56-year-old woman was diagnosed with persistent trophoblastic disease after her hCG levels remained high following surgery for evacuation of a complete molar pregnancy. She was commenced on treatment with methotrexate but after three cycles her hCG levels had failed to fall appropriately and she was changed to the more intensive EMA-CO regimen. On commencing the first day of etoposide in the first cycle of EMA-CO the patient developed sudden onset facial flushing, lip tingling, chest tightness and retrosternal/back pain within 2 min of the infusion. Her symptoms resolved with discontinuing the infusion and treatment with intravenous chlorpheniramine (10 mg) and hydrocortisone (100 mg).

The following day chemotherapy was recommenced using Etopophos as an alternative. Within 4 min of the infusion she again developed facial and upper limb flushing, central chest pain, back pain and dyspnoea. The infusion was stopped and she was successfully treated with intravenous chlorpheniramine and hydrocortisone. The symptoms of chest pain and flushing resolved initially but the back pain continued. Within 15 min the facial flushing recurred so she was treated with further hydrocortisone and remained well after this.

Following this, the patient's treatment was changed to single agent actinomycin-D and after seven cycles of successful treatment, her hCG levels had fallen to normal. After completing an additional three cycles of consolidation therapy the hCG levels have remained normal for 18 months and the patient is almost certainly cured of her illness.

Case 2

A 22-year-old female was diagnosed with a choriocarcinoma nine weeks following an in utero death at 38

weeks' gestation. Her hCG level was 230,000 IU/L and on CT she was found to have multiple pulmonary metastases. She was commenced on emergency low-dose induction chemotherapy with etoposide and cisplatin which was subsequently switched to the EMA-CO regimen. The first three cycles of treatment were well tolerated and the hCG levels were falling satisfactorily. On the fourth cycle of chemotherapy, however, she had an allergic reaction to etoposide. After 5 min of the infusion of etoposide the patient developed sudden onset chest tightness and shortness of breath. The infusion was stopped and emergency treatment with intravenous hydrocortisone and chlorpheniramine was delivered. The following day the patient was rechallenged with Etopophos; however, after 10 min of the infusion severe chest tightness occurred again. The infusion was discontinued and treatment was required with hydrocortisone and chlorpheniramine.

Following this event the patient was successfully treated with a modified EMA (without etoposide)-CO regime and on follow up she remains in remission.

Discussion

Etoposide is an important chemotherapy agent used in the treatment of many cancers and has a central role in treating curable malignancies, particularly testicular tumours and gestational trophoblastic disease. However, etoposide use is associated with a rare but clinically important risk of serious allergic reactions. In most cases the patient develops a reaction within the first 5–10 min of receiving the infusion and complete recovery is usual once the infusion is discontinued. There have also been reports of hypersensitivity reactions occurring several hours after administration.⁶ If continued treatment with etoposide is considered essential for the disease then further doses can be trialled at a slower rate, using premedication with steroids and antihistamines. Despite this, around 22% of patients will remain intolerant to etoposide.¹²

Etopophos was developed to overcome solubility problems with etoposide, as etoposide is poorly soluble in water and therefore administration of large doses can require large fluid volumes.⁸ Being water soluble, Etopophos can be made up to concentrations of 20 mg/ml and can be given as a 5-min bolus, as a high dose in small volume and as a continuous infusion.¹³ A further advantage of Etopophos is the lack of documented hypersensitivity and it was thus rendered a safe alternative in patients who had experienced an allergic reaction to etoposide.^{3,6,9,10} It has previously been suggested that the lack of hypersensitivity to Etopophos is because it does not contain the polysorbate solvent found in intravenous etoposide.

This is supported by the lack of documented allergic reactions to oral etoposide and until recently, the lack of hypersensitivity reactions to Etopophos.

Our data and the recently published case of anaphylaxis to Etopophos¹⁰ show that patients can have an additional hypersensitivity reaction to Etopophos. This suggests that the reaction is likely due to the etoposide molecule itself, rather than the polysorbate solvent. In the study where administration of polysorbate was found to induce histamine release, hypotension and tachycardia in dogs, it was shown that the tachycardia induced with polysorbate was much weaker than that with etoposide, suggesting that etoposide was at least in part responsible.¹¹

As a result we continue to offer Etopophos as standard treatment to patients with etoposide allergy but do so with the first administration taking place under medical supervision.

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